August 30, 2018

Ms. Monet Vela
Office of Environmental Health Hazard Assessment
P.O. Box. 4010
Sacramento, CA 95812-4010

Submitted electronically via oeeha.ca.gov/comments

Re: Proposed Adoption of New Section Under Article 7 No Significant Risk Levels, Section 25704 Exposures to Listed Chemicals in Coffee Posing No Significant Risk

Dear Ms. Vela:

The National Coffee Association ("NCA") appreciates the opportunity to submit comments regarding the Office of Environmental Health Hazard Assessment's Notice of Proposed Rulemaking, Proposed Adoption of New Section Under Article 7 No Significant Risk Levels, Section 25704 Exposures to Listed Chemicals in Coffee Posing No Significant Risk dated June 22, 2018. Established in 1911, NCA is the largest and oldest national coffee trade association consisting of over three hundred coffee manufacturers, importers, distributors, and retailers, most of whom serve Californians' demand for coffee. NCA members are comprised of organizations from across the industry and represent more than 1,694,710 jobs in the U.S. economy alone.

As discussed in further detail below, OEHHA's Rulemaking is supported by both the full weight of scientific evidence and law. From a scientific standpoint, the Rulemaking is based on the International Agency for Research on Cancer's recent conclusion that there is insufficient evidence to classify coffee as carcinogenic and that coffee consumption is actually associated with a reduced risk of certain cancers. The attached letter—signed by Dr. Mark Corey, NCA's Director of Scientific & Government Affairs, and Dr. Alan Leviton, Consultant to the NCA Scientific Advisory Group—explains why the comments raised by the Council for Education and Research on Toxics at the August 16, 2018 public hearing are misguided and do nothing to call into question the scientific basis upon which OEHHA's Rulemaking is based. The letter also brings to OEHHA's attention recent scientific studies of coffee and cancer that further support OEHHA's determination that exposures to Proposition 65 listed chemicals in coffee that are produced as part of and inherent in the processes of roasting coffee beans and brewing coffee pose no significant risk of cancer. Because IARC's and OEHHA's determinations relate to the carcinogenicity of *coffee* as a whole, and not to any individual chemical component of coffee, our scientific comments focus on science regarding coffee. Discussions about the

carcinogenicity of an individual chemical such as acrylamide—a chemical which was subject to a separate regulatory process years ago—are irrelevant to this Rulemaking. From a legal standpoint, OEHHA's Rulemaking is well within OEHHA's statutory authority and furthers the purpose of Proposition 65 by avoiding inaccurate and unnecessary warnings for a widely consumed and beneficial product.

NCA supports Proposition 65's purpose of ensuring that consumers are warned about exposures that cause cancer or reproductive harm. But if Proposition 65's purpose is to be achieved in a meaningful way, NCA believes it is equally important to ensure that consumers are *not* warned for exposures that *do not* cause cancer or reproductive harm. Indeed, NCA believes that this Rulemaking furthers this purpose, as it will avoid a proliferation of Proposition 65 warnings on coffee, a product that the scientific community has overwhelmingly concluded does not cause cancer. Any other outcome would frustrate the scientific, legal, and policy rationales upon which Proposition 65 is based. Accordingly, NCA supports the Rulemaking and requests that OEHHA adopt it without modification.

In addition, NCA requests that OEHHA adopt the Rulemaking as promptly as possible. There are some retailers who are already providing Proposition 65 warnings for coffee in light of pending litigation, the risk of extreme penalties, and possible future litigation. Once consumers are warned about a product, the resulting mental impression is very difficult to reverse; it is akin to a bell that cannot be un-rung. The prospect of additional warnings, with the potential for even greater consumer confusion, requires prompt action from OEHHA.

OEHHA's Proposal Is Well Within Its Statutory Authority And Furthers The Purposes Of Proposition 65.

As the agency tasked with implementing Proposition 65, OEHHA is empowered to "adopt and modify regulations, standards, and permits as necessary to conform with and implement this chapter and to further its purposes." Health and Safety Code section 25249.12, subd. (a). Health and Safety Code section 25249.10, subdivision (c) further provides that the obligation to warn "shall not apply to . . . [a]n exposure for which the person responsible can show that the exposure poses no significant risk assuming lifetime exposure at the level in question for substances known to the state to cause cancer . . . based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of such chemical." In the more than thirty years since Proposition 65 was enacted, OEHHA has adopted regulations defining these terms and has otherwise implemented Proposition 65 in accordance with its statutory authority.

OEHHA Has The Statutory Authority To Set Exposure Levels For Which No Warning Is Required.

From the earliest days of Proposition 65's implementation, OEHHA has adopted regulatory "safe harbor" levels for individual listed substances, numerical levels of exposure below which no Proposition 65 warnings are required. Final Statement of Reasons, 22 Cal. Code Regs. Div. 2, Sections 12701 *et seq.* and 12801 *et seq.* (June 1989), at p. 28 (noting that OEHHA may adopt safe harbor levels and that "[t]he authority to adopt regulations implementing the Act rests with the lead agency"). The safe harbor regulations have provided meaningful guidance to

"persons in the course of doing business" so that they can either reduce the level of listed substances in their products or provide warnings, thereby reducing the number of warnings that are provided simply to prevent litigation without reference to whether they are required under Proposition 65. Indeed, the California Court of Appeal recently noted this important role in upholding OEHHA's longstanding safe harbor level for lead, one of the most widely litigated listed chemicals. *Mateel Env't Justice Found. v. OEHHA*, 24 Cal. App. 5th 220, 235-36 (2018) (approving safe harbor level for lead and holding that "[w]e cannot say that in adopting a MADL of 0.5 micrograms per day the Agency acted in a manner that was 'arbitrary, capricious, or entirely lacking in evidentiary support'" and "Mateel has failed to show OEHHA's determination that 30 micrograms/100g blood lead level will have 'no observable effect' was arbitrary or capricious").

OEHHA Has The Statutory Authority To Take Action With Respect To Entire Classes Of Listed Substances.

Indeed, OEHHA has the statutory authority to adopt regulations that apply across a category of listed substances, and OEHHA has appropriately exercised this authority with respect to far broader categories of substances found in foods. In *Nicolle-Wagner v. Deukmejian*, 230 Cal. App. 3d 652 (1991), a plaintiff challenged a regulation enacted by OEHHA's predecessor, the Health and Welfare Agency (the "Agency"), that exempted naturally occurring chemicals in food from Proposition 65's warning requirement. Cal. Code Regs., tit. 22, § 12501. The trial court held that the Agency had acted within the scope of its statutory authority in enacting the regulation, and the Court of Appeal affirmed, holding that the regulation reasonably promoted the statutory purposes of Proposition 65.

First, the Court of Appeal looked at the ballot pamphlet for Proposition 65 to determine the intent of the voters and noted that proponents of the law made clear that it was intended to apply to chemicals that are "put into the environment by human activity." *Nicolle-Wagner*, 230 Cal. App. 3d at 659. The Court saw this distinction—between chemicals that are naturally occurring in foods and chemicals that are added to foods—as significant, and as a distinction that supported the Agency's exemption for naturally occurring chemicals in foods. *Id.*

Second, the *Nicolle-Wagner* Court noted that without an exemption for naturally occurring chemicals in foods, "grocers and others would be required, in order to avoid liability under these statutes, to post a warning label on most, if not all, food products." *Id.* at 661. Indeed, the Agency had previously observed in its Final Statement of Reasons that the "[a]bsence of such an exemption could unnecessarily reduce the availability of certain foods or could lead to unnecessary warnings, which could distract the public from other important warnings on consumer products." *Id.* Thus, the Court of Appeal determined the exemption for naturally occurring chemicals would "further the statutory purpose in safeguarding the effectiveness of warnings which are given, and in removing from regulatory scrutiny those substances which pose only an 'insignificant risk' of cancer or birth defects, within the meaning of the statute." *Id.*

In addition to the naturally occurring exemption that was upheld in *Nicolle-Wagner*, OEHHA's predecessor has exercised its authority to adopt regulations that provide complete exemptions for exposures to certain chemicals in foods by adopting the "cooking provision." Under this

provision, exposures to listed carcinogens are entitled to a higher, alternative form of the "no significant risk level" when supported by "sound considerations of public health . . . as, for example . . . where chemicals in food are produced by cooking necessary to render the food palatable or to avoid microbiological contamination." Cal. Code Regs., tit. 27, § 25703(b)(1). This regulation has never been challenged, but it is clearly valid under the rationale adopted in *Nicolle-Wagner*. In the Final Statement of Reasons, the Agency noted that "there is extensive information in the scientific literature which indicates that chemicals having mutagenic and/or carcinogenic properties are formed as a result of cooking food" and "[t]he confusion that would result if all purveyors of cooked or heat-processed foods provide a warning with their product, to avoid any potential liability, could be enormous."

It is therefore well within OEHHA's statutory authority to enact the Rulemaking stating that exposures to listed chemicals in coffee that are produced as part of and inherent in the processes of roasting coffee beans or brewing coffee pose no significant risk of cancer. OEHHA's Proposal is based on extensive scientific data from the International Agency for Research on Cancer ("IARC"), one of the authoritative bodies for the identification of listed chemicals. Cal. Code Regs., tit. 28, § 25306, subd. (l)(1). **After reviewing more than 1,000 studies of coffee and cancer, IARC concluded that there is insufficient evidence to classify coffee as carcinogenic and that coffee consumption is associated with a reduced risk of certain cancers.** OEHHA's determination that there is no significant risk of cancer from exposure to chemicals in coffee that are created by roasting or brewing is therefore based on sufficient scientific evidence.

Indeed, under the cooking provision adopted by OEHHA's predecessor to implement Proposition 65, a court has the authority to determine that an alternative significant risk level is appropriate for a chemical created in cooking food. Likewise, OEHHA retains that same authority and could state a numerical level for an individual chemical, such as acrylamide, created in cooking a type of food, such as coffee, where supported by "sound considerations of public health." Here, such sound considerations clearly exist as to not only acrylamide, but also as to all chemicals in coffee that are produced as part of and inherent in the processes of roasting coffee beans and brewing coffee, not only due to the risk of over-warning, but also due to the overwhelming strength of scientific evidence showing that drinking coffee does not increase the risk of cancer in humans.

OEHHA Has The Statutory Authority To Set An Infinite "No Significant Risk Level".

Furthermore, nothing in Proposition 65 or its implementing regulations indicates that a "no significant risk level" must be stated numerically or even be finite. OEHHA's Rulemaking is the practical equivalent of a finding that the "no significant risk level" for carcinogens in coffee that are produced as part of and inherent in the processes of roasting and brewing coffee is infinite. It does not affect the listing of these chemicals, which is controlled expressly by statutory requirements, but instead interprets and implements the express statutory exemption from warnings where "the exposure poses no significant risk assuming lifetime exposure at the level in question." In *Baxter Healthcare Corp. v. Denton*, 120 Cal. App. 4th 333 (2004), the Court of Appeal approved of a trial court finding that any level of exposure to a chemical requires no Proposition 65 warning because the chemical, although properly listed on the basis of animal studies, does not affect humans in the same manner. The *Baxter* court essentially

adopted an infinite safe harbor level for the chemical, based on the strength of scientific evidence. Just as a court is permitted to do this, so is OEHHA.

OEHHA's Rulemaking Furthers The Purposes Of Proposition 65 By Avoiding Unnecessary Warnings.

OEHHA's Rulemaking furthers the purposes of Proposition 65 by avoiding unnecessary warnings for chemicals in coffee that are created by roasting or brewing. A principle purpose of Proposition 65 is to provide clear and reasonable warnings, but warnings are meaningless—and indeed, frustrate the purpose of Proposition 65—if they are provided for exposures to chemicals in products that pose no significant cancer risk. Warnings that are inconsistently given for the same food product, moreover, confuse the public, discourage consumption of healthful products, and undermine the public confidence in Proposition 65. Here, as documented in OEHHA's ISOR and in the attached letter, it is well-established that coffee does not increase the risk of cancer, and may even reduce the risk of cancer in some circumstances. Providing a cancer warning on coffee, therefore, would be the epitome of over-warning, a result that undermines the public interest and the goal of Proposition 65 to provide warnings for risks that are not insignificant.

OEHHA's Rulemaking Furthers The Purposes Of Proposition 65 Because It Is Appropriately Tailored To Coffee.

The Rulemaking is appropriately tailored to a single product: coffee. It is not a blanket or categorical exemption for all chemicals in all foods. Only Proposition 65 listed chemicals in coffee that are produced as part of and inherent in the processes of roasting coffee beans and brewing coffee would be deemed to pose no significant risk of cancer. OEHHA's determination that such exposures pose no significant risk of cancer is fully supported by IARC's conclusion that there is inadequate evidence for the carcinogenicity of coffee to humans and that coffee consumption is associated with a reduced risk of certain cancers. OEHHA tailored a regulation that affects *only* chemicals that are created by roasting or brewing, and *only* those chemicals in coffee, a product that has been extensively studied and for which such chemicals pose no significant risk of cancer. Because IARC's and OEHHA's determinations relate to the carcinogenicity of *coffee* as a whole, and not to any individual chemical component of coffee, discussions about the carcinogenicity of an individual chemical such as acrylamide are irrelevant to this Rulemaking. And unlike other proposed regulations that have been challenged as overbroad categorical exemptions, OEHHA's Rulemaking is narrow, precise, and based on a robust body of scientific studies that are specific to the chemicals and product at issue.

Contrary to CERT's assertions, the 1990 trial court decision by then Judge Ronald Robie in *AFL-CIO v. Deukmejian* (Duke II), is inapplicable to the Rulemaking here. In *Duke II*, the regulation at issue would have exempted *all chemicals* in all foods, drugs, cosmetics, and medical devices based solely on their compliance with unidentified federal and state standards and with no scientific hazard analysis concerning the products, the chemicals, or the exposures at issue. In settling that case, the defendants agreed to use specific numeric standards for chemicals when setting a no significant risk level that is based on federal or state standards:

> Defendants agree that any provision which is adopted after the date of this agreement to define the term "no significant risk" of the Act for any food, drug, cosmetic or medical device product, and ***which employs standards derived from existing state or federal law*** shall be based upon scientific numeric standards for the chemical, as evidenced by the rulemaking file.

Duke II Settlement Agreement (Case No. 502541, Dec. 23, 1992) (emphasis added). The *Duke II* settlement is inapplicable to this Rulemaking because the proposed regulation is not based on any "standards derived from existing state or federal law." Rather, the Rulemaking is based on the International Agency for Research on Cancer's recent conclusion that there is insufficient evidence to classify coffee as carcinogenic and that coffee consumption is actually associated with a reduced risk of certain cancers.

OEHHA's Rulemaking Furthers The Purposes Of Proposition 65 By Not Affecting Any Obligation To Warn For Chemicals In Coffee That Are Intentionally Added.

In addition, the Rulemaking furthers the purpose of Proposition 65 because, consistent with voter intent, it does not affect any obligation to warn for chemicals that are intentionally added to coffee. As noted by the *Nicolle-Wagner* court, the arguments for and against the 1986 ballot measure demonstrate that the law is aimed at chemicals that are intentionally added to products. The ballot argument in favor of Proposition 65 explains, "These new laws . . . apply only to businesses that *know* they are putting one of the chemicals out into the environment, and that *know* the chemical is actually on the Governor's list." Similarly, the ballot argument against Proposition 65 refers to "manmade carcinogens" as the target of the new law: "The simple *scientific fact* of the matter is that manmade carcinogens represent only a tiny fraction of the total carcinogens we are exposed to, most of which are natural substances such as tobacco, alcohol, and chemicals in green plants. Significant amounts of manmade carcinogens are highly regulated in California under the most stringent laws in the United States. This initiative will result in chasing after trivial amounts of manmade carcinogens at *enormous cost* with minimal benefit to our health." Just as these statements of voter intent supported the *Nicolle-Wagner* court's upholding of the naturally occurring exemption, they support OEHHA's Rulemaking on coffee.

Thus, the Rulemaking would further the purpose of Proposition 65 because it would clarify that warnings are unnecessary for chemicals in coffee that are inherently created by the roasting or brewing process, but, consistent with ballot initiative materials and the original intent of the law, would not exempt chemicals that may be intentionally added to coffee.

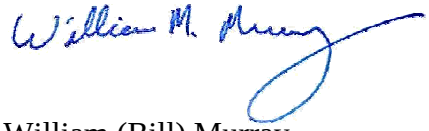
* * *

OEHHA's Rulemaking is supported by both science and law. It is well within OEHHA's statutory authority and furthers the purpose of Proposition 65 by avoiding inaccurate and unnecessary warnings for a widely consumed and beneficial product while preserving any obligation to warn for chemicals that are intentionally added to coffee. And as discussed in the attached letter from experts in the scientific community, the new cancer-related studies

published since IARC's review further supports OEHHA's determination that coffee consumption does not cause cancer in humans and reduces incidences of certain cancers.

Thank you for considering our comments. We appreciate the opportunity to participate in this very important regulatory process and urge OEHHA to adopt the Rulemaking as soon as practicable.

Sincerely,



William (Bill) Murray
President & CEO
National Coffee Association, USA

Attachment

This scientific commentary is submitted as part of the National Coffee Association's comment letter regarding the Office of Environmental Health Hazard Assessment's determination that exposures to Proposition 65 listed chemicals in coffee that are produced as part of and inherent in the process of roasting coffee beans and brewing coffee pose no significant risk of cancer. As a scientific matter, we support OEHHA's Rulemaking and believe it is based on sound and well-established scientific principles. To this end, we have concerns with several of the arguments made by Council for Education and Research on Toxics at the August 16, 2018 public hearing because they are either false, misleading, or irrelevant. Accordingly, in this commentary we very briefly address several of CERT's arguments and explain why they are flawed and should be rejected by OEHHA. Additionally, although OEHHA's reliance on IARC's review is more than sufficient to support the Rulemaking, for OEHHA's convenience, we have prepared a summary of all of the new cancer-related studies published since IARC's review, the totality of which further supports OEHHA's determination that coffee consumption does not cause cancer in humans and reduces incidences of certain cancers.

CERT's Comments From The Public Hearing

1. **CERT's Comment:** In concluding that coffee has not been found to increase the risk of any cancers, OEHHA misinterprets the IARC monograph. IARC did not reach this conclusion, but rather, reported significantly increased risks for a number of human cancers, especially childhood leukemia from maternal consumption of coffee during pregnancy. Significantly increased risks of cancer from consumption of coffee have also been reported for bladder cancer, esophageal cancer, gastric cancer, laryngeal cancer, lung cancer, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, and total cancer.

   Response: Where individual reports occasionally indicate increased risk of malignancy, almost invariably the authors acknowledge residual confounding may have occurred. *See* Tables 1-15 below. In particular, if a malignancy is already a recognized tobacco-related malignancy site, residual confounding factors remain the most likely explanation for increased risk. Isolated reports have been published of increased risks of some malignancies associated with coffee consumption, but many more and/or larger and better conducted studies have not found increased risks. IARC itself noted: "If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound." IARC Monographs Volume 116: Evaluation of drinking coffee, maté, and very hot beverages, p. 19.

   Regarding childhood cancers, although leukemias are viewed as the most common malignancies among children (< 19 years of age), their age-adjusted incidence is still < 5/100,000.[1] Because prospective studies of the offspring of pregnant women have not been sufficiently large to provide an adequate number

[1] Barrington-Trimis JL, Cockburn M, Metayer C, Gauderman WJ, Wiemels J, McKean-Cowdin R. Trends in childhood leukemia incidence over two decades from 1992 to 2013. Int J Cancer. 2017 Mar 1;140(5):1000-1008.

of childhood leukemias for a powerful cohort study, there were no cohort studies for IARC to review. Thus, all seven of the published reports reviewed by IARC investigating the potential association between maternal coffee consumption during pregnancy and childhood leukemias were case-control studies. Three of the seven did not find any statistically significant relationship.[2,3,4] One study that was reviewed (Menegaux et al., 2005) indicated a relationship but only for consumption by the mother of $\geq$ 4 cups/day.[5] Two other reports IARC reviewed found relationships at lower levels of consumption.[6,7] One of the older reports which IARC reviewed that investigated maternal coffee consumption was a study by Ross et al., 1998.[8] This study investigated consumption of coffee during pregnancy by asking women more than 10 years after the pregnancy to recall what they drank while pregnant. The study consisted of three separate studies, only one of which found a statistically significant relationship between maternal coffee consumption and childhood leukemia, and then only at consumption levels of 4 or more cups per day. In summary, three of the seven studies reviewed by IARC found that maternal coffee consumption was associated with increased risk of childhood leukemia in the offspring, and three did not, while one had mixed findings. This is likely why, regarding childhood leukemias, IARC themselves concluded in the monograph: "**The lack of consistency among the findings of the studies, particularly those conducted within the same country by the same group, led the Working Group to evaluate the evidence for this site as inconclusive."**

---

[2] Petridou E, Trichopoulos D, Kalapothaki V, Pourtsidis A, Kogevinas M, Kalmanti M, Koliouskas D, Kosmidis H, Panagiotou JP, Piperopoulou F, Tzortzatou F. The risk profile of childhood leukaemia in Greece: a nationwide case-control study. Br J Cancer. 1997;76(9):1241-7.

[3] Menegaux F, Ripert M, Hemon D, Clavel J Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: a French population-based case-control study. Paediatr Perinat Epidemiol 2007;21:293–299.

[4] Milne E, Royle JA, Bennett LC, de Klerk NH, Bailey HD, Bower C, Miller M, Attia J, Scott RJ, Kirby M, Armstrong BK. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: results from an Australian case-control study. Cancer Causes Control 2011;22:207–218.

[5] Menegaux F, Steffen C, Bellec S, Baruchel A, Lescoeur B, Leverger G, Nelken B, Philippe N, Sommelet D, Hemon D, Clavel J. Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. Cancer Detect Prev 2005;29:487–493.

[6] Bonaventure A, Rudant J, Goujon-Bellec S, Orsi L, Leverger G, Baruchel A, Bertrand Y, Nelken B, Pasquet M, Michel G, Sirvent N, Bordigoni P, Ducassou S, Rialland X, Zelenika D, Hemon D, Clavel J. Childhood acute leukemia, maternal beverage intake during pregnancy, and metabolic polymorphisms. Cancer Causes Control 2013;24:783–793.

[7] Orsi L, Rudant J, Ajrouche R, Leverger G, Baruchel A, Nelken B, Pasquet M, Michel G, Bertrand Y, Ducassou S, Gandemer V, Lutz P, Saumet L, Moreau P, Hemon D, Clavel J. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: the ESTELLE study. Cancer Causes Control 2015;26:1003–1017.

[8] Ross JA. Maternal diet and infant leukemia: a role for DNA topoisomerase II inhibitors? Int J Cancer Suppl. 1998;11:26-8.

In regards to some of the challenges related to interpreting results from these case control studies, one meta-analysis[9] included the statement, "[t]he available case-control studies … are characterized by great heterogeneity, in terms of methodology, types of leukemia studied -namely total AL (all acute leukemia), ALL (acute lymphoblastic leukemia), acute myeloid leukemia (AML) or infant leukemia-, sample size, statistical analysis and control for potential confounding factors." Another meta-analysis[10] suggested that different results can occur when participants recall coffee consumption habits from being interviewed versus answering questions on a questionnaire. The authors went on to state that they "noted the positive association between coffee consumption and childhood ALL and childhood AML among studies using interviewing techniques, but not among studies using self-administrated questionnaire. The contrast may [be] due to a consequence of information bias (mainly recall bias) because of different assessment techniques used in different studies." This is possible, especially if mothers of children who had leukemia did not report all their smoking to the interviewer, but were truthful when completing the self-administered questionnaire, a phenomenon identified as "socially desirable responding."[11,12] Other biases are also likely, for example, compared to the mothers of healthy newborns, mothers of children with a major congenital malformation diagnosed soon after birth preferentially recalled exposures or characteristics during the index pregnancy.[13] This type of "recall bias" plagues any study that compares recall of exposure during pregnancy by mothers who have given birth to a child with a serious disorder to the recall by mothers who have given birth to a healthy child (or a child without a serious disorder). In light of all these considerations, we caution the assumption that maternal coffee consumption during the pregnancy influences the child's risk of leukemia or any other serious disorder.

2. **CERT's Comment:** OEHHA assumes that inverse associations noted by IARC between coffee consumption and some cancers in observational studies are causal. IARC made no such determination, and instead concluded that "the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer."

---

[9] Thomopoulos TP, Ntouvelis E, Diamantaras AA, Tzanoudaki M, Baka M, Hatzipantelis E, Kourti M, Polychronopoulou S, Sidi V, Stiakaki E, Moschovi M, Kantzanou M, Petridou ET. Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis. Cancer Epidemiol. 2015; 39(6):1047-59.

[10] Cheng J, Su H, Zhu R, et al. Maternal coffee consumption during pregnancy and risk of childhood acute leukemia: a metaanalysis. Am J Obstet Gynecol 2014; 210(2):151 e151-151 e110.

[11] Contzen N, De Pasquale S, Mosler HJ. Over-Reporting in Handwashing Self-Reports: Potential Explanatory Factors and Alternative Measurements. PLoS One 2015;10(8):e0136445.

[12] Bornstein MH, Putnick DL, Lansford JE, et al. Mother and father socially desirable responding in nine countries: Two kinds of agreement and relations to parenting self-reports. Int J Psychol 2015; 50(3):174-185.

[13] Werler MM, Pober BR, Nelson K, et al. Reporting accuracy among mothers of malformed and nonmalformed infants. Am J Epidemiol 1989; 129(2):415-421.

Response: This is false. Even the most sophisticated epidemiology study design is incapable of determining causation. That is precisely why those who evaluate observation studies that associate exposures with human disease bend over backwards to avoid causal statements. *See, e.g.*, Wakeford R. Association and causation in epidemiology - half a century since the publication of Bradford Hill's interpretational guidance. J R Soc Med. 2015;108(1):4-6; Dammann O. The Etiological Stance: Explaining Illness Occurrence. Perspect Biol Med. 2017;60(2):151-165.; Dammann O. Hill's Heuristics and Explanatory Coherentism in Epidemiology. Am J Epidemiol. 2018; 187(1):1-6.

3. **CERT's Comment:** OEHHA claims that antioxidants in coffee prevent human cancer. But IARC never made any such conclusion. Neither IARC nor any reputable scientific organization has ever concluded that antioxidants prevent human cancer.

Response: This is false. There is substantial evidence that antioxidants can be "chemopreventive agents" that have the capacity to "control cancer incidence." *See* Mohsenzadegan M, Seif F, Farajollahi MM, Khoshmirsafa M. Anti-Oxidants as Chemopreventive Agents in Prostate Cancer: A Gap Between Preclinical and Clinical Studies. Recent Pat Anticancer Drug Discov. 2018; 13(2):224-239. Martinez-Useros J, Li W, Cabeza-Morales M, Garcia-Foncillas J. Oxidative Stress: A New Target for Pancreatic Cancer Prognosis and Treatment. J Clin Med. 2017;6(3), pii: E29; Selim KA, Abdelrasoul H, Aboelmagd M, Tawila AM. The Role of the MAPK Signaling, Topoisomerase and Dietary Bioactives in Controlling Cancer Incidence. Diseases. 2017; 5(2). pii: E13.

4. **CERT's Comment:** Meta-analyses of randomized controlled trials show that antioxidant intake actually causes some human cancers, rather than reducing human cancer. The mechanism by which antioxidants are hypothesized to prevent cancer (destruction of free radicals) is not relevant to the mechanism (genotoxicity and in particular clastogenicity) by which acrylamide causes cancer.

Response: This is misleading. First, antioxidants do not "actually cause some human cancers." Rather, smokers and asbestos workers given specific isolated anti-oxidants had higher rates of adverse effects than those not given these individual compounds with antioxidant effects. *See* Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammar S. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 1996; 334(18):1150-5; Lippman SM, Lee JJ, Karp DD, Vokes EE, Benner SE, Goodman GE, Khuri FR, Marks R, Winn RJ, Fry W, Graziano SL, Gandara DR, Okawara G, Woodhouse CL, Williams B, Perez C, Kim HW, Lotan R, Roth JA, Hong WK. Randomized phase III intergroup trial of isotretinoin to prevent second primary tumors in stage I non-small-cell lung cancer. J Natl Cancer Inst. 2001; 93(8):605-18. Second, those studies were of supplements and not dietary antioxidants. Retinoids, the compounds given in these clinical trials, have many

other effects besides anti-oxidants. *See* Omenn GS. Review Chemoprevention of lung cancers: lessons from CARET, the beta-carotene and retinol efficacy trial, and prospects for the future. Eur J Cancer Prev. 2007 Jun; 16(3):184-91; Fritz H, Kennedy D, Fergusson D, Fernandes R, Doucette S, Cooley K, Seely A, Sagar S, Wong R, Seely D. Vitamin A and retinoid derivatives for lung cancer: a systematic review and meta-analysis. PLoS One. 2011; 6(6):e21107.

5. **CERT's Comment:** In the two years since IARC completed its review in May 2016, several epidemiology studies, specially designed to determine whether the inverse associations between coffee consumption and various chronic diseases (including cancer) are causal, have been published. These epidemiology studies used a sophisticated study design that is capable of determining causation.

   Response: This is false. *See* Response to CERT's Comment No. 2.

6. **CERT's Comment:** These studies provide strong scientific evidence that the inverse associations between coffee consumption and chronic diseases and cancer, as reported in observational studies, are not causal, but are instead artefactual.

   Response: This is misleading. It is true that these studies do not show causation. Yet, they are also clearly not artefactual. The categories of likely causal, highly likely the exposure and the outcome are related (but not necessarily causal), uncertain relationship between exposure and outcome, etc. are deemed arbitrary. Artefactual is only one of many possible categories. Indeed, some prefer to see relationships between an exposure and an outcome along a continuum. *See* Haslam N, Kim HC. Categories and continua: a review of taxometric research. Genet Soc Gen Psychol Monogr 2002; 128(3):271-320; Katsanis N. The continuum of causality in human genetic disorders. Genome Biol. 2016; 17:233; Hernán MA. Does water kill? A call for less casual causal inferences; Ann Epidemiol. 2016; 26(10):674–680; Pearce N, Lawlor DA. Causal inference—so much more than statistics. Int J Epidemiol. 2016;45(6):1895–1903; VanderWeele TJ. Commentary: On Causes, Causal Inference, and Potential Outcomes. Int J Epidemiol. 2016; 45(6):1809–1816.

7. **CERT's Comment:** These studies show that the inverse associations for coffee and chronic diseases are likely due to confounding and reverse causation.

   Response: Some studies may be more biased than others. On the other hand, large scale, high quality epidemiologic studies tend to be relatively free of the common potential biases. An approach to dealing with conflicting findings from different studies that is now favored by some assesses "the weight of evidence." *See* Linkov I, Loney D, Cormier S, Satterstrom FK, Bridges T. Weight-of-evidence evaluation in environmental assessment: review of qualitative and quantitative approaches. Sci Total Environ. 2009 Sep 15; 407(19):5199-205; Rhomberg L. Hypothesis-Based Weight of Evidence: An Approach to Assessing

Causation and its Application to Regulatory Toxicology. Risk Anal 2015; 35(6):1114-24; Lutter R, Abbott L, Becker R, Borgert C, Bradley A, Charnley G, Dudley S, Felsot A, Golden N, Gray G, Juberg D, Mitchell M, Rachman N, Rhomberg L, Solomon K, Sundlof S, Willett K. Improving weight of evidence approaches to chemical evaluations. Risk Anal. 2015 Feb; 35(2):186-92; Bailey LA, Nascarella MA, Kerper LE, Rhomberg LR. Hypothesis-based weight-of-evidence evaluation and risk assessment for naphthalene carcinogenesis. Crit Rev Toxicol. 2016; 46(1):1-42. Indeed, the IARC monograph has the following quote: "The Working Group's review gave the greatest weight to data from well-conducted prospective cohort studies." IARC Monographs Volume 116: Evaluation of drinking coffee, maté, and very hot beverages, p. 301.

8. **CERT's Comment:** OEHHA writes: "Coffee is unique in that it shows reductions in certain human cancers, has not been shown to increase any cancers, and is particularly rich in cancer chemo-preventive compounds." This statement is scientifically incorrect, because the same is true of tobacco!

   Response: This is false. No one can say that tobacco "has not been shown to increase any cancers." Indeed, a review has the following statements: "There is evidence for an established association of tobacco use with cancer of the lung and larynx, head and neck, bladder, oesophagus, pancreas, stomach and kidney. … There are some data suggesting that tobacco use increases the risk for myeloid leukaemia, squamous cell sinonasal cancer, liver cancer, cervical cancer, colorectal cancer after an extended latency, childhood cancers and cancer of the gall bladder, adrenal gland and small intestine." Kuper H, Boffetta P, Adami HO. Tobacco use and cancer causation: association by tumour type. J Intern Med. 2002; 252(3):206-24.

9. **CERT's Comment:** OEHHA failed to consider negative confounding by cigarette smoke as a biological explanation for the inverse association between coffee consumption and endometrial cancer. OEHHA incorrectly assumed that coffee consumption prevents endometrial cancer.

   Response: Page 241 of the IARC Monograph explains: "As BMI and smoking are important confounders, studies not adjusting for these factors (Jacobsen et al. 1986; Levi et al., 1993b; Stensvold & Jacobsen 1994; Goodman et al., 1997; Bravi et al., 2009b) were considered uninformative and were excluded from further review." Thus, studies that might have been confounded by cigarette smoking were eliminated from consideration.

10. **CERT's Comment:** Because coffee is naturally bitter, it is typically consumed with sugars, sweeteners, creamers, whiteners, flavorings, and other additives. These additives are not healthy. They contain high levels of sugars and saturated fat, which are known to significantly increase the risk of cardiovascular diseases. Cardiovascular disease is a major risk factor for cancer.

Response: This claim is not based on scientific evidence. Despite all these additives, coffee drinkers are *not* at increased risk of cardiovascular diseases. *See* Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation. 2014;129(6):643-59; Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Annu Rev Nutr. 2017;37:131-156; Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ. 2017;359:j5024; Rodríguez-Artalejo F, López-García E. Coffee Consumption and Cardiovascular Disease: A Condensed Review of Epidemiological Evidence and Mechanisms. J Agric Food Chem. 2018;66(21):5257-5263. This reduced risk of cardiovascular diseases may contribute to the reduced risk of cancer among coffee drinkers.

11. **CERT's Comment:** Coffee causes adverse pregnancy outcomes, including reduced fetal weight and growth, pregnancy loss (including spontaneous abortion and stillbirth), infertility (in both men and women), and adverse effects in children and adolescents.

Response: Most of the studies linking maternal coffee consumption and fetal adversities are flawed. *See* Leviton A. Biases Inherent in Studies of Coffee Consumption in Early Pregnancy and the Risks of Subsequent Events. Preprints 2018, 2018070467. Therefore, inferences should not be drawn about the link between coffee consumption and fetal weight or pregnancy loss.

A recent review of the relationships between coffee (and caffeine) consumption and indicators of male fertility concluded, "[e]vidence from epidemiological studies on semen parameters and fertility is however inconsistent and inconclusive." Ricci E, Viganò P, Cipriani S, Somigliana E, Chiaffarino F, Bulfoni A, Parazzini F. Coffee and caffeine intake and male infertility: a systematic review. Nutr J. 2017; 16(1):37. Another recent review addressing coffee consumption effects on women and men concluded, "there seems to be little, if any, association between coffee/caffeine consumption and fecundity." Lyngsø J, Ramlau-Hansen CH, Bay B, Ingerslev HJ, Hulman A, Kesmodel US. Association between coffee or caffeine consumption and fecundity and fertility: a systematic review and dose-response meta-analysis. Clin Epidemiol. 2017; 9:699-719.

Although daily high caffeine intakes (e.g. >5 mg/kg body weight day) by children have been associated with an increased risk of anxiety and withdrawal symptoms, "smaller amounts were not linked with such effects and may benefit cognitive function and sports performance based on adult studies." Ruxton CH. The suitability of caffeinated drinks for children: a systematic review of randomised controlled trials, observational studies and expert panel guidelines. J Hum Nutr Diet. 2014; 27(4):342-57.

Years after high-risk very-premature newborns were given caffeine when they were in the intensive care nursery, they have more favorable motor and cognitive functions than their peers who were given another drug or placebo. *See* Schmidt B, Roberts RS, Anderson PJ, Asztalos EV, Costantini L, Davis PG, Dewey D, D'Ilario J, Doyle LW, Grunau RE, Moddemann D, Nelson H, Ohlsson A, Solimano A, Tin W; Caffeine for Apnea of Prematurity (CAP) Trial Group. Academic Performance, Motor Function, and Behavior 11 Years After Neonatal Caffeine Citrate Therapy for Apnea of Prematurity: An 11-Year Follow-up of the CAP Randomized Clinical Trial. JAMA Pediatr. 2017 Jun 1; 171(6):564-572; Khurana S, Shivakumar M, Sujith Kumar Reddy GV, Jayashree P, Ramesh Bhat Y, Lewis LES. Long-term neurodevelopment outcome of caffeine versus aminophylline therapy for apnea of prematurity. J Neonatal Perinatal Med. 2017; 10(4):355-362.

12. **CERT's Comment:** Coffee consumption increases the risk of developing several chronic diseases: bone disease (osteoporosis and fractures), cardiovascular diseases (coronary heart disease, myocardial infarction, stroke, heart failure, and angina pectoris), autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes), gastrointestinal disorders (constipation, gallstones, and gastroesophageal reflux disease), urological conditions (urolithiasis, lower urinary tract symptoms, urinary incontinence, and urinary tract infections), acute cardiovascular events within 1 hour of consumption.

    Response: "Coffee consumption was more often associated with benefit than harm for a range of health outcomes across exposures including high versus low, any versus none, and one extra cup a day." Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ. 2017; 359:j5024.

    "Given the spectrum of conditions studied and the robustness of many of the results, these findings indicate that coffee can be part of a healthful diet." Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Annu Rev Nutr. 2017; 37:131-156.

Summary of New Cancer-Related Studies

Since IARC first published its 2016 summary of the final evaluations concerning the carcinogenicity of drinking coffee, additional scientific studies concerning coffee and cancer have been published. The totality of the studies further supports OEHHA's determination that coffee consumption does not cause cancer in humans and reduces incidences of certain cancers. Where individual reports occasionally indicate increased risk of malignancy, almost invariably, the authors acknowledge residual confounding may have occurred. In particular, if a malignancy is already a recognized tobacco-related malignancy site, residual confounding factors remain the most likely explanation for increased risk. With this in mind, we have shared where the authors have pointed this out in their studies.

The weight of the evidence continues to favor the view that coffee consumption provides benefits. For example, coffee drinkers live longer than non-coffee drinkers. For OEHHA's convenience, all of the new cancer-related studies published since IARC's review are briefly summarized below, organized by cancer site.[14] Copies of these studies can be provided upon request:

1. Multiple Cancer Sites

Since the IARC working group met in 2016, 18 scientific studies have been published on the relationship between coffee consumption and risk of cancer of multiple sites and/or all-cause mortality. These studies are listed in Table 1. Additionally, some brief highlights are noted here. In particular, it is important to note that since the IARC working group met in 2016, two umbrella reviews about coffee consumption and multiple health outcomes have been published. In 2017, Grosso et al. published "Coffee, Caffeine, and Health Outcomes: An Umbrella Review". The authors evaluated 59 unique health outcomes. The study found that coffee is associated with a probable decreased risk of certain cancers, including breast, colorectal, colon, endometrial, and prostate cancers, as well as decreased risk of mortality, and the authors concluded that "coffee can be part of a healthful diet."

A similarly robust review by Poole et al., 2017 concluded that consumption of coffee was associated with a decreased risk of certain cancers and generally safe within usual consumption levels. The authors stated, "Coffee consumption seems generally safe within usual levels of intake, with summary estimates indicating largest risk reduction for various health outcomes at three to four cups a day, and more likely to benefit health than harm." However, overall, the evidence strongly suggests that people who drink coffee are less likely to develop cancer, and in general, live longer than non-coffee drinkers. Thus, as can be seen in the table below, the weight of the evidence continues to favor the view that not only does coffee consumption reduce the risk of selected malignancies, but also all-site cancer mortality.

Table 1. Studies on coffee consumption and multiple cancer sites and/or all-cause mortality

Title & reference	Type of Study/ cancer sites	Author's conclusions & additional perspective
"Coffee consumption and mortality from all causes of death, cardiovascular disease and cancer in an elderly Spanish population" Torres-Collado L, Garcia-de-la-Hera M, Navarrete-Munoz EM, Notario-Barandiaran L, Gonzalez-Palacios S, Zurriago O, Melchor I, Vioque J Eur J	Cohort	"No significant association was observed with all cause or cancer mortality, neither for caffeinated and decaffeinated coffee."

[14] Studies identified herein were publicly available as of August 26, 2018.

Title & reference	Type of Study/ cancer sites	Author's conclusions & additional perspective
Nutr 2018 in press Aug		
"Association of Coffee Drinking With Mortality by Genetic Variation in Caffeine Metabolism: Finsings From the UK Biobank" Loftfield E, Cornelis MC, Caporaso N, Yu K, Sinha R, Freedman N JAMA Intern Med 2018 Jul. 2	Prospective Cohort	The authors concluded "Coffee drinking was inversely associated with mortality, including among those drinking 8 or more cups per day and those with genetic polymorphisms indicating slower or faster caffeine metabolism." Authors did note that limitations included low participation rate but that their "results reflect those from prior studies in different populations worldwide."
"Association of coffee, tea and caffeine intake with risk of breast, endometrial and ovarian cancer among Canadian women" Arthur A, Kirsh VA, Rohan TE Cancer Epidemiology 2018 56: 75-82	Prospective Cohort Looked at Breast Endometrial Ovarian	The authors concluded "In this prospective study, coffee, tea and caffeine intake were not associated with overall risk of breast and ovarian cancers. However, our findings suggested that increasing levels of total coffee, caffeinated coffee and/or caffeine may be associated with increased risk of breast cancer among premenopausal and normal weight women. In contrast total coffee, caffeinated coffee and caffeine were inversely associated with risk of endometrial cancer." The authors go on to state that "The observed weak positive associations of total, caffeinated coffee and or caffeine intake with risk of breast cancer among premenopausal and normal weight women are possibly due to chance." And "…there is consistent evidence, both from the present study and from previous studies, of an inverse association of total and caffeinated coffee intake with risk of endometrial cancer."

Title & reference	Type of Study/ cancer sites	Author's conclusions & additional perspective
"Coffee consumption and risk of rare cancers in Scandinavian countries" Lukic M, Nilsson LM, Skeie G, Lindahl B, Braaten T Eur J Epidemiol. 2018 Feb. 23.	Prospective cohort Looked at bladder, esophageal, kidney, pancreatic and stomach cancer among Norwegian women	"Our data suggest that increased filtered coffee consumption might reduce the risk of pancreatic cancer. We did not find evidence of an association between coffee consumption and the risk of esophageal or kidney cancer. The increased risk of bladder and stomach cancer was confined to never smokers." Cigarette smoking is associated with malignancies at both of these sites, raising the probability of residual confounding. Indeed, the authors wrote, "Finally, residual confounding of some factors cannot be ruled out." The authors go on to note in relation to the finding of increased risk "the analyses were hampered by the small number of cases."
Prospective study of coffee consumption and cancer incidence in non-white populations Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW Cancer Epidemiol Biomarkers Prev. 2018 Aug;27(8):928-935.	Prospective Cohort Coffee; caffeine; cancer; liver, ovarian, thyroid and endometrial cancers and melanoma	Prospective study of coffee consumption and cancer incidence in non-white populations. Assessed 34,031 cases of cancer. Authors conclude coffee drinking may protect against liver, ovarian, thyroid and endometrial cancers.
"Coffee or Tea? A prospective cohort study on the associations of coffee and tea intake with overall and cause-specific mortality in men versus women" Van den Brandt Eur J Epidemiol. 2018 Jan. 27.	Prospective Cohort Overall cause specific morality	"Higher coffee intake was significantly, nonlinearly related to lower overall and cause-specific mortality in women. In men, coffee was significantly positively related to cancer and cardiovascular mortality, and inversely related to respiratory and other causes of death." The authors go on to state "the possibility of residual confounding by smoking or confounding by unmeasured factors remains."

Title & reference	Type of Study/ cancer sites	Author's conclusions & additional perspective
"Coffee and cancer risk: a summary overview" Alicandro G, Tavani A, La Vecchia C Eur J Cancer Prev. 2017 Mar. 10.	Review of meta-analyses and collaborative re-analyses	"The data considered in this review indicate that coffee consumption is not associated with an increased risk of any cancer, including most common cancer sites, such as lung, breast, and prostate cancers."
"Protective effect of coffee consumption on all cause mortality of French HIV-HCV co-infected patients" Carrieri MP, Protopopescu C, Marcellin F, Rosellini S, Wittkop L, Esterle L, Zucman D, Raffi F, Rosenthal E, Poizot-Martin I, Salmon-Ceron D, Dabis F, Spire B, the ANRS CO13 HEPAVIH Study Group; J Hepatol 2017 67(6): 1157-1167	Prospective Cohort	HIV – human immunodeficiency virus HCV – hepatitis C virus "This study shows that elevated coffee consumption ($\geq$ 3 cups/day) halves all-cause mortality risk in patients co-infected with HIV-HCV.
Associations of Coffee Drinking and Cancer Mortality in the Cancer Prevention Study-II Gapstur SM, Anderson RL, Campbell PT, Jacobs EJ, Hartman TJ, Hildebrand JS, Wang Y, McCullough ML Cancer Epidemiol Biomarkers Prev. 2017 Jul. 27	Prospective Cohort Colorectal Liver Female breast Head and neck Esophageal	"These findings are consistent with many other studies that suggest coffee drinking is associated with a lower risk of colorectal, liver, female breast and head and neck cancer. The association of coffee consumption with higher risk of esophageal cancer among nonsmokers in our study should be confirmed." "Results from this study demonstrate residual confounding by smoking on the association between coffee consumption and cancer risk particularly among current smokers."
Coffee, Caffeine, and Health Outcomes: An Umbrella Review Grosso G, Godos J, Galvano F, Giovannucci EL Annu Rev	Umbrella Review (review of meta-analyses of observational studies, and randomized	Looked at 59 unique outcomes and concluded that "given the spectrum of conditions studied and the robustness of many of the results, these findings indicate that coffee can be part of a

Title & reference	Type of Study/ cancer sites	Author's conclusions & additional perspective
Nutr. 2017 Aug. 21; 37:131-156	controlled trials (RCTs))	healthful diet."
Coffee consumption and selected gastrointestinal cancers morbidity in Poland Jarosz M., Rychlik E., Sekula W. Annals of Nutrition and Metabolism 2017 71 Supplement 2 (984) -poster	Meta-analysis Liver Gallbladder Colorectal	"The increase in coffee consumption in Poland could favourably affect some gastrointestinal cancers such as liver and gallbladder cancer morbidity rates in Poland and probably was one of the reasons of the observed decline in these cancers incidence in recent years."
A review of caffeine use as a risk or protective factor for women's health and pregnancy Peacock A., Mattick R.P., Bruno R.	Review	Coffee and lower risk of cancer is discussed but in the context of caffeine.
Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. BMJ. 2017 Nov. 22; 359:j5024	Umbrella Review of observational and interventional studies of coffee consumption and any health outcome	"Coffee consumption seems generally safe within usual levels of intake, with summary estimates indicating largest risk reduction for various health outcomes at three to four cups a day, and more likely to benefit health than harm."
Association between coffee consumption and all-sites cancer incidence and mortality Sado J, Kitamura T, Kitamura Y, Sobue T, Nishino Y, Tanaka H, Nakayama T, Tsuji I, Ito H, Suzuki T, Katanoda K, Tominaga S. Cancer Sci. 2017 Jul. 26.	Prospective Cohort	"We showed an inverse association between frequency of coffee consumption and all-sites cancer incidence in both men and women." Comparing participants who consumed coffee with those who never drank coffee, "Coffee consumption frequency was inversely associated with mortality from all sites cancer. In this population, increasing coffee consumption resulted in a decreased risk of all-sites cancer incidence and mortality."
Coffee consumption and risk of all-cause, cardiovascular,	Review- meta-	"[C]offee consumption is associated with decreased risk of mortality from

Title & reference	Type of Study/ cancer sites	Author's conclusions & additional perspective
and cancer mortality in smokers and non-smokers: a dose-response meta-analysis Grosso G, Micek A, Godos J, Sciacca S, Pajak A, Martínez-González MA, Giovannucci EL, Galvano F. Eur J Epidemiol. 2016 Oct. 3	analysis	all-cause, CVD, and cancer; however, smoking modifies the observed risk when studying the role of coffee on human health."
Coffee consumption and mortality in three Eastern European countries: results from the HAPIEE (Health, Alcohol and Psychosocial factors In Eastern Europe) study Grosso G, Stepaniak U, Micek A, Stefler D, Bobak M, Pajak A Public Health Nutr. 2016 Jul. 14:1-10	Prospective Cohort	"Coffee consumption was associated with decreased risk of mortality. The protective effect was even stronger when stratification by smoking status and alcohol intake was performed."
Coffee intake, cardiovascular disease and all cause mortality: observational and Mendelian randomization analyses in 95000-223000 individuals Nordestgaard AT and Nordestgaard BG Int. J. Epidemiol 2016; 45(6): 1938-1952	Population-based observational study	"[O]bservationally, coffee intake was associated with U-shaped lower risk of ….all cause mortality." "[G]enetically coffee intake was not associated with all-cause mortality."
A Comprehensive Overview of the Risks and Benefits of Coffee Consumption Pourshahidi LK, Navarini L, Petracco M, Strain JJ Institute of Food Technologists®	Review	"This qualitative assessment has shown that the health benefits (or null effects) clearly outweigh the risks of moderate coffee consumption in adult consumers for the majority of health outcomes considered. Results from this research may aid further qualitative and quantitative deterministic risk–benefit assessments of coffee consumption."

2. Bladder Cancer

In our surveillance of the literature post-IARC (from 2016-2018) there have been two studies published that addressed the relationship between coffee consumption and bladder cancer in Japanese, American, and European populations. These studies found that coffee was associated with increased risk, but cautioned that residual confounding may play a role (people under report smoking and smoking is a known cause of bladder cancer).

Table 2. Studies on coffee consumption and bladder cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
"Coffee consumption and risk of rare cancers in Scandinavian countries" Lukic M, Nilsson LM, Skeie G, Lindahl B, Braaten T. Eur J Epidemiol. 2018 Mar.; 33(3):287-302. doi: 10.1007/s10654-018-0369-9	Prospective cohort	"The increased risk of bladder and stomach cancer was confined to never smokers." The authors go on to note "subgroup analyses by smoking status … lacked statistical power in the analyses of bladder, esophageal and stomach cancer sites, and this problem was more pronounced in the analyses of never smokers." Further, these findings were deemed non-significant as the authors state, "[w]e did not observe significant associations between total or boiled coffee consumption and any of the investigated cancer sites, neither in the entire study sample nor in the analyses stratified by sex." In essence, their findings were NOT statistically significant.
"A prospective investigation of coffee drinking and bladder cancer incidence in the United States" Loftfield E, Freedman ND, Inoue-Choi M, Graubard BI, Sinha R. Epidemiology. 2017 Sept.; 28(5):685-693.	Prospective cohort	"Coffee drinking was positively associated with bladder cancer in models adjusted for age and sex;" however, they found "no evidence of an association among never smokers." Therefore, the authors concluded that "residual confounding from imperfect measurement of smoking may explain their positive findings." This is an example of a tobacco related malignancy.

3. Blood Cancer

In our surveillance of the literature post-IARC (from 2016-2018) there have been six studies published that addressed the relationship between coffee consumption and blood cancers, including leukemia, myeloma, and lymphoma. IARC concluded at the time of their review that data for this endpoint were inconclusive. Of the six studies published since IARC's review, five of the studies found no significant association between coffee consumption and risk of certain types of leukemia or other blood cancers, and one (Parodi et al.) found an enhanced risk of lymphoma among heavy coffee drinkers, which, according to authors, was "without a clear dose-response trend" and required further investigation "to confirm the observed observation." In addition, exposure level was determined by interview after the diagnosis and thus results may be influenced by recall bias, in which people who have the disease are more likely to report the exposure of interest.

Table 3. Studies on coffee consumption and blood cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Maternal Consumption of coffee and tea during pregnancy and risk of childhood ALL: a pooled analysis from the childhood Leukemia International Consortium Milne E, Greenop KR, Petridou E, Bailey HD, Orsi L, Kang AY, Baka M, Bonaventure A, Kourti M, Metayer C, Clavel J Cancer Causes and Control. 2018 Mar.	Pooled case control	"Despite this international collaborative effort, our pooled analysis lacked the statistical power to allow firm conclusions to be drawn, particularly regarding associations within subgroups, and the results should be interpreted with caution."
Coffee and green tea consumption and subsequent risk of acute myeloid leukemia and myelodysplastic syndromes in Japan. Ugai T., Matsuo K., Sawada N., Iwasaki M., Yamaji T., Shimazu T., Goto A., Inoue M., Kanda Y., Tsugane S. International Journal of Cancer. 2018; 142:6 (1130-1138).	Population-based prospective cohort study (95,807 subjects; 85 Acute Myeloid Leukemia cases and 70 Myelodysplastic syndrome (MDS) cases)	"Our findings showed no significant association between coffee consumption and the risk of AML." However, the authors "observed a …. dose-response relationship between coffee consumption and the risk of MDS among men," with rates of MDS being lower among higher coffee drinkers. The authors further noted: "Stratified analysis by smoking status suggested that the observed relative risk for AML and MDS of coffee drinkers relative to non-coffee drinkers might be due to residual confounding by

Title & Reference	Type of Study	Author's conclusions & additional perspective
		smoking."
Coffee and tea consumption and risk of leukaemia in an adult population: A reanalysis of the Italian multicentre case-control study. Parodi S, Merlo DF, Stagnaro E. Cancer Epidemiol. 2017 Jan. 30;47:81-87.	Case-control study. Italian population; 1771 controls and 651 leukaemia cases.	"No association was observed between regular use of coffee and any type of leukaemia." The authors concluded: "The lower risk of leukaemia among regular coffee consumers, reported by a few of previous small studies, was not confirmed." Regarding the limitations of their study, authors listed lack of information on the type of coffee consumed; unknown consumption for former coffee drinkers; and recall and selection bias.
Coffee and Green Tea Consumption and Subsequent Risk of Malignant Lymphoma and Multiple Myeloma in Japan: The Japan Public Health Center-based Prospective Study. Ugai T, Matsuo K, Sawada N, Iwasaki M, Yamaji T, Shimazu T, Sasazuki S, Inoue M, Kanda Y, Tsugane S. Cancer Epidemiol Biomarkers Prev. 2017 Aug; 26(8):1352-1356.	Population-based prospective cohort study (95,807 subjects; 411 malignant lymphoma cases and 138 multiple myeloma cases	acute myeloid leukemia (AML) myelodysplastic syndromes (MDS) "In this study, we observed no significant association between coffee …. consumption and the risk of malignant lymphoma or multiple myeloma." "We observed an inverse association between-coffee consumption and the risk of MDS among Japanese men." "No significant association was observed between coffee and the risk of AML. The observed relative risk for AML/MDS of coffee drinkers relative to non-coffee drinkers might be due to residual confounding by smoking."
Coffee consumption and risk of non-Hodgkin's lymphoma: evidence from the Italian multicentre case-control study. Parodi S, Merlo FD, Stagnaro E. Cancer Causes Control. 2017 Jun. 13.	Case-control study. Italian population; 1,301 B cell and 117 T cell NHL cases.	"Consumption of more than four cups of coffee per day enhances the risk of lymphoma, especially the follicular subtype. Further investigations based on large cohorts and accurate measures of exposure are needed to confirm the observed associations."

Title & Reference	Type of Study	Author's conclusions & additional perspective
		"For all B cell lymphomas, an increased risk (OR 1.6, 95% CI 1.2-2.0) was observed in the highest exposure category (consumption >4 cups per day for at least 30 years), but without a clear dose-response trend." The lack of a dose-response trend indicates that coffee consumption is unlikely to contribute to the occurrence of B cell lymphomas. In addition, the authors listed as limitations of their study lack of information on the type of coffee consumed; unknown consumption for former coffee drinkers; incomplete classification of NHL; and recall bias.
Coffee and the Risk of Lymphoma: A Meta-analysis Article. Han T, Li J, Wang L, Xu H. Iran J Public Health. 2016 Sept.; 45(9):1126-1135.	Meta-analysis; included studies from USA, Europe, and Asia	"There was no sufficient evidence to support coffee consumption association with the risk of lymphoma. Further well-designed large-scaled cohort studies are needed to provide conclusions that are more definitive."

4. Brain Cancer

Three recent studies since IARC's review focus on the association between coffee consumption and brain cancer, with particular attention to brain tumors and glioma. No association was found between maternal coffee intake and risk of childhood brain tumors, and these studies saw an inverse association between coffee consumption and risk of glioma (*e.g.*, higher coffee consumption was associated with lower cancer risk).

Table 4. Studies on coffee consumption and brain cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Parental smoking, maternal alcohol, coffee and tea consumption and the risk of childhood brain tumours: the ESTELLE and ESCALE studies (SFCE, France).	Case-control studies (pooled analysis); 510 cases of CBT	CBT = childhood brain tumor Mothers of children with CBT and controls) were interviewed by telephone to determine exposure status. Authors reported: "No association was seen

Title & Reference	Type of Study	Author's conclusions & additional perspective
Bailey H.D., Lacour B., Guerrini-Rousseau L., Bertozzi A.-I., Leblond P., Faure-Conter C., Pellier I., Freycon C., Doz F., Puget S., Ducassou S., Orsi L., Clavel J. Cancer Causes Control 2017; 28:7 (719-732).		between CBT and the mother smoking or drinking alcohol, coffee, or tea during the index pregnancy."
Tea and coffee consumption in relation to glioma: a case-control study. Malmir H, Shayanfar M, Mohammad-Shirazi M, Tabibi H, Sharifi G, Esmaillzadeh A. Eur J Nutr. 2017 Nov. 9.	Case-control study	"We found that… coffee consumption was inversely associated with glioma such that . . . individuals in the top category of coffee consumption were 91% less likely to have glioma compared with those in the bottom category."
Coffee and green tea consumption in relation to brain tumor risk in a Japanese population. Ogawa T, Sawada N, Iwasaki M, Budhathoki S, Hidaka A, Yamaji T, Shimazu T, Sasazuki S, Narita Y, Tsugane S. Int J Cancer. 2016 Aug. 25.	Prospective cohort study in Japanese population; 106,324 subjects, 157 cases.	The authors concluded, "our study suggested that coffee consumption might reduce the risk of brain tumor[s], including that of glioma, in the Japanese population." "In this study, we found a significant inverse association between coffee and brain tumor risk. Furthermore, glioma risk tended to decrease with higher coffee consumption."

5. Breast Cancer

In our surveillance of the literature post-IARC (from 2016-2018) there have been eight studies published that addressed the relationship between coffee consumption and breast cancer. Populations included women in Turkey, Norway, United Kingdom, Canada, and the United States, and study designs included meta-analyses, cohorts, and case-control designs. Five studies conclude that coffee consumption is inversely associated with risk of breast cancer, although effect sizes were small. One of those five studies, while concluding that, overall, coffee consumption was not associated with increased breast cancer risk, suggests that "coffee consumption might be associated with increased breast cancer risk in women who used hormones in the past" (Yaghiyan 2018). Another study found an increased risk of breast cancer among premenopausal women drinking 3-4 cups of caffeinated coffee per day, but the risk was not elevated for women drinking less than 3 or more than 4 cups per day. The authors discuss

the lack of confidence in the strength of association (Arthur 2018). Overall, the weight of the evidence suggests no association between coffee intake and breast cancer.

Table 5. Studies on coffee consumption and breast cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Associations of coffee, tea and caffeine intake with risk of breast, endometrial and ovarian cancer among Canadian women Arthur R., Kirsh V.A., Rohan T.E. Cancer Epidemiol. 2018; 56: (75-82)	Prospective cohort	"Coffee, tea, and caffeine intake were not associated with overall risk of breast and ovarian cancers. There was, however, a tendency towards an increased risk of breast cancer with increasing levels of total coffee, caffeinated coffee and/or caffeine among premenopausal and normal weight women." However, the association does not exhibit a dose-response relationship and authors "lacked detailed information on the preparation methods and varieties of these beverages, and therefore, we were not able to fully account for these factors in our analyses. This may have resulted in misclassification of the exposures of interest, which would have influenced the strength of the association observed."
Coffee Intake Decreases Risk of Postmenopausal Breast Cancer: A Dose-Response Meta-Analysis on Prospective Cohort Studies. Lafranconi A, Micek A, De Paoli P, Bimonte S, Rossi P, Quagliariello V, Berretta M. Nutrients. 2018 Jan. 23; 10(2).	Meta-analysis	"Findings from this meta-analysis may support the hypothesis that coffee consumption is associated with decreased risk of postmenopausal breast cancer." The authors concluded that "overall we observed no significant association between coffee intake and breast cancer risk but coffee consumption may represent a protective factor for post-menopausal breast cancer risk. Further evidences taking into account population subsets and specific strata are extremely needed to corroborate the retrieved associations."

Title & Reference	Type of Study	Author's conclusions & additional perspective
Interactions of coffee consumption and postmenopausal hormone use in relation to breast cancer risk in UK Biobank. Yaghjyan L, Rich S, Mao L, Mai V, Egan KM Cancer Causes Control. 2018 Apr. 12. doi: 10.1007/s10552-018-1028-x.	Case-control	PMH = post-menopausal hormone "While we did not observe any associations in the overall analysis, our findings suggest that coffee consumption might be associated with an increased breast cancer risk in women who used postmenopausal hormones in the past. However, in the absence of any association among current PMH users, these findings are inconsistent with our hypothesis and likely represent a chance finding."
An Adolescent and Early Adulthood Dietary Pattern Associated with Inflammation and the Incidence of Breast Cancer. Harris HR, Willett WC, Vaidya RL, Michels KB Cancer Res. 2017 Mar. 1; 77(5):1179-1187. doi: 10.1158/0008-5472.CAN-16-2273.	Prospective cohort	"Overall, our findings support the notion that an adolescent and early adulthood diet characterized by high intake of …. coffee may increase the incidence of premenopausal breast cancer." The authors acknowledge that "[a]nother limitation is that diet during high school was self-reported-by participants when they were 33–52 years old and some error in its measurement is expected."
Dietary factors modify post-menopausal breast cancer risk: A case-control study from Turkish Cypriot population. Pervaiz R., Tosun Ö., Besim H ., Serakinci N. Biomedical Research and Therapy 2017; 4:3 (1171-1184)	Case-control	BC= breast cancer Authors concluded that "no significant association [was] observed between consumption of … coffee intake and BC risk."
Coffee intake and risk of breast and ovarian cancer: Updated systematic review and meta-analysis. Bamia C., Turati F., Guercio	Meta-analysis	"Findings from this updated meta-analysis suggest a weak inverse association with breast cancer." "Given the high consumption of coffee

Title & Reference	Type of Study	Author's conclusions & additional perspective
V., Guha N., Loomis D., Tavani A. Annals of Nutrition and Metabolism 2017; 71 Supplement 2 (950-951).		worldwide these results may be of high public health importance."
Associations of Coffee Drinking and Cancer Mortality in the Cancer Prevention Study-II. Gapstur SM, Anderson RL, Campbell PT, Jacobs EJ, Hartman TJ, Hildebrand JS, Wang Y, McCullough ML Cancer Epidemiol Biomarkers Prev. 2017 Jul. 27.	Cohort	"These findings are consistent with many other studies that suggest coffee drinking is associated with a lower risk of … female breast … cancer." "We observed an inverse relationship between coffee consumption and breast cancer mortality (i.e., risk decreased by 3% per 2 cups/day increase) which is consistent with a study of cancer incidence from the European Prospective Investigation into Nutrition and Cancer (EPIC)."
Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Grosso G, Godos J, Galvano F, Giovannucci EL Annu Rev Nutr. 2017 Aug. 21; 37:131-156.	Review	According to the authors, "coffee was associated with a probable decreased risk of breast [cancer]." Given the spectrum of conditions studied and the robustness of many of the results, these findings indicate that coffee can be part of a healthful diet."

6. Esophageal Cancer

In our surveillance of the literature published since the IARC re-evaluation, there have been five studies looking at the relationship between coffee consumption and esophageal cancer. The findings are not consistent but the weight of the evidence suggest no association.

Table 6. Studies on coffee consumption and esophageal cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Coffee consumption and risk of esophageal cancer incidence Zhang J., Zhou B., Hao C. Medicine (United States)	Meta-analysis	"When stratified by sex, pathologic type of esophageal cancer, and type of epidemiologic study, we did not find any association of coffee consumption and esophageal cancer incidence." However, authors found a protective

Title & Reference	Type of Study	Author's conclusions & additional perspective
2018; 97:17		role of coffee consumption against esophageal cancer in East Asians (but not in Euro-Americans). Authors questioned whether unknown temperature of coffee when consumed may affect results.
Coffee consumption and risk of rare cancers in Scandinavian countries Lukic M, Nilsson LM, Skeie G, Lindahl B, Braaten T Eur J Epidemiol 2018 Feb. 23.	Prospective cohort	"We did not find evidence of an association between coffee consumption and the risk of esophageal….cancer."
Risk factors for progression of Barrett's esophagus to high grade dysplasia and esophageal adenocarcinoma: A large retrospective cohort study (abstract). Kambhampati S., Luber B., Wang H., Meltzer S.J. Gastroenterology 2017 152:5 Supplement 1 (S455).	Retrospective cohort	This large retrospective cohort study validated known risk factors including age, abdominal obesity, and smoking history but also identified several novel risk factors, including history of regurgitation, solid organ transplantation, colonic adenomas, and caffeine usage. Only an abstract was available and thus not yet peer reviewed. The abstract had only abbreviated conclusions and limitations.
Associations of Coffee Drinking and Cancer Mortality in the Cancer Prevention Study-II Gapstur SM, Anderson RL, Campbell PT, Jacobs EJ, Hartman TJ, Hildebrand JS, Wang Y, McCullough ML Cancer Epidemiol Biomarkers Prev 2017	Cohort	"The association of coffee consumption with higher risk of esophageal cancer among nonsmokers in our study should be confirmed." "In a recent WCRF/AICR systematic literature review of five prospective studies there was no association between coffee and esophageal cancer risk." "The positive association between coffee consumption and esophageal cancer mortality found in our study might be due to chance or confounding by unknown factors. Alternatively, coffee might increase esophageal cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
		risk through an inflammatory mechanism as a result of reflux; however, there is inconsistent evidence on the role of coffee consumption in gastro-esophageal reflux disease."
Coffee and Cancer risk: a summary overview Alicandro G, Tavani A, La Vcchia C Eur J Cancer Prev 2017	Review	"Although based on very few studies and a very limited number of cases, no relation was found for cancers of the esophagus."

7. Kidney Cancer

Two recent studies since the IARC evaluation (one case-control study and one meta-analysis) discussed the association between coffee consumption and renal cell carcinoma (RCC). Antwi, et al. found that while caffeinated coffee consumption was associated with a reduced risk of RCC, decaffeinated coffee was actually associated with an increased risk of both RCC and an aggressive subtype (clear cell RCC or ccRCC). However, the meta-analysis study (Wijarnpreecha, et al.) did not find any significant association between coffee consumption and RCC, and concluded that coffee intake is not a risk factor for RCC.

Table 7. Studies on coffee consumption and kidney cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Coffee consumption and risk of renal cell carcinoma. Antwi SO, Eckel-Passow JE, Diehl ND, Serie DJ, Custer KM, Arnold ML, Wu KJ, Cheville JC, Thiel DD, Leibovich BC, Parker AS Cancer Causes Control. 2017 Jun. 24.	Case-control; 669 cases of renal cell carcinoma (RCC)	RCC = renal cell carcinoma "Consumption of caffeinated coffee is associated with reduced risk of RCC, while decaffeinated coffee consumption is associated with an increase in risk of aggressive RCC. Further inquiry is warranted in large prospective studies and should include assessment of dose-response associations." The authors suggest that "Further studies are needed to validate these findings and explore possible mechanisms underlying the associations, particularly the suggestive interactions

Title & Reference	Type of Study	Author's conclusions & additional perspective
		with alcohol consumption and hypertension status."
Association between coffee consumption and risk of renal cell carcinoma: A Meta-analysis. Wijarnpreecha K, Thongprayoon C, Thamcharoen N, Panjawatanan P, Cheungpasitporn W Intern Med J. 2017 Sept. 11.	Meta-analysis	"Our study demonstrates no significant association between coffee consumption and RCC. Thus, coffee consumption is likely not a risk factor for RCC. Whether coffee consumption has a potential role in reduced risk of RCC, particularly in males, requires further investigations."

8. Cancer of the Large Intestine

In our surveillance of the literature post-IARC (from 2016-2018) there have been 15 studies looking at the relationship between coffee and colon cancer. Nearly all of the studies found an inverse association with coffee consumption and risk of colorectal cancer. It was common for authors to use phrases such as "coffee as a prevention option," "coffee can be part of a healthful diet," and "coffee might reduce cancer progression." Reviews were the prominent type of study identified and hundreds of thousands of people were followed with tens of thousands of cases of colon cancer studied. A number of different populations were studied, including Spanish, Japanese, Polish, American and Israeli. Although this was a category whereby not all studies came to the same conclusion, the overwhelming majority and hence the weight of the evidence suggested that coffee consumption (generally higher intake) was associated with lower risk of colorectal cancer.

Table 8. Studies on coffee consumption and colon cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Association study of dietary non-enzymatic antioxidant capacity (NEAC) and colorectal cancer risk in the Spanish Multicase-Control Cancer (MCC-Spain) study. Amiano P, Molina-Montes E, Molinuevo A, Huerta JM, Romaguera D, Gracia E, Martín V, Castaño-Vinyals G, Pérez-Gómez B, Moreno V, Castilla J, Gómez-Acebo I,	Case-control	"Findings of this large case-control study on the association between dietary NEAC intake and colorectal cancer (CRC) risk support the idea that CRC risk is reduced by intake of an antioxidant-rich diet." "NEAC from coffee represents the main source of dietary NEAC in several populations, including ours."

Title & Reference	Type of Study	Author's conclusions & additional perspective
Jiménez-Moleón JJ, Fernández-Tardón G, Chirlaque MD, Capelo R, Salas L, Azpiri M, Fernández-Villa T, Bessa X, Aragonés N, Obón-Santacana M, Guevara M, Dierssen-Sotos T, Barrios-Rodríguez R, de la Torre AJM, Vega AB, Pollán M, Kogevinas M, Sánchez MJ Eur J Nutr. 2018 Jul. 11. Epub ahead of print		
A Dose-Response Meta-analysis of Coffee Consumption and Colorectal Cancer Risk in the Japanese Population: Application of a Cubic-Spline Model. Horisaki K, Takahashi K, Ito H, Matsui S J Epidemiol. 2018 Jun. 2. Epub ahead of print	Meta-analysis	"In this study, a meta-analysis of cohort studies indicated that associations between coffee consumption and CRC were not significant, whereas meta-analysis of case-control studies suggested an inverse association in the Japanese population." "From the results of the present dose-response meta-analysis, we conclude that there is insufficient evidence to support the hypothesis that coffee drinking either increases or decreases CRC risk among the Japanese population. Moreover, our results suggest that mild coffee consumption may not be associated with or only weakly inversely associated with the risk of CRC, although its influence is not statistically significant."
Coffee drinking and colorectal cancer and its subsites: A pooled analysis of 8 cohort studies in Japan. Kashino I, Akter S, Mizoue T, Sawada N, Kotemori A, Matsuo K, Oze I, Ito H, Naito M, Nakayama T, Kitamura Y, Tamakoshi A, Tsuji I, Sugawara Y, Inoue M, Nagata	Meta-analysis	The authors conclude that "this pooled analysis of data from large prospective studies in Japan with considerable number of subjects and incident colorectal cancer cases found no association between coffee drinking and colorectal cancer in men or women. In site specific analysis, coffee drinking was significantly and inversely

Title & Reference	Type of Study	Author's conclusions & additional perspective
C, Sadakane A, Tanaka K, Tsugane S, Shimazu T; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Int J Cancer. 2018 Jul. 15:143(2): 307-316.		associated with colon cancer in women."
Coffee and cancer risk: a summary overview. Alicandro G, Tavani A, La Vecchia C Eur J Cancer Prev. 2017 Sept. 26(5): 424-432.	Review of meta-analyses and collaborative reanalyses	The authors state that "although coffee has shown a favorable effect in case–control studies, the inconsistent association found in cohort studies does not allow conclusions on the relation of coffee intake and colorectal cancer risk, although an increased risk can be excluded."
Association of coffee consumption with risk of colorectal cancer: A meta-analysis of prospective cohort studies. Gan Y., Wu J., Zhang S., Li L., Cao S., Mkandawire N., Ji K., Herath C., Gao C., Xu H., Zhou Y., Song X., Chen S., Chen Y., Yang T., Li J., Qiao Y., Hu S., Yin X., Lu Z. Oncotarget 2017 8:12 (18699-18711).	Meta-analysis	The authors conclude that "coffee consumption is significantly associated with a decreased risk of colorectal cancer at ≥ 5 cups per day of coffee consumption. The findings support the recommendations of including coffee as a healthy beverage for the prevention of colorectal cancer."
Associations of Coffee Drinking and Cancer Mortality in the Cancer Prevention Study-II. Gapstur SM, Anderson RL, Campbell PT, Jacobs EJ, Hartman TJ, Hildebrand JS, Wang Y, McCullough ML Cancer Epidemiol Biomarkers Prev. 2017 Oct. 26(10):1477-1486.	Prospective cohort	"Coffee consumption also may be inversely associated with risk of colorectal cancer."

Title & Reference	Type of Study	Author's conclusions & additional perspective
Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Grosso G, Godos J, Galvano F, Giovannucci EL Annu Rev Nutr. 2017 Aug. 21; 37:131-156.	Umbrella Review/meta-analysis	"The evidence for coffee was assessed as probable for the association of decreased risks for….. colorectal and colon cancers."
Association Between Coffee Intake After Diagnosis of Colorectal Cancer and Reduced mortality. Hu Y, Ding M, Yuan C, Wu K, Smith-Warner SA, Hu FB, Chan AT, Meyerhardt JA, Ogino S, Fuchs CS, Giovannucci EL, Song M Gastroenterology. 2018 Mar.; 154(4):916-926	Prospective cohort	"In an analysis data from the Nurses' Health Study and Health Professionals Follow-up Study, we associated intake of caffeinated and decaffeinated coffee after diagnosis of CRC with lower risk of CRC-specific death and overall death. Studies are needed to determine the mechanisms by which coffee might reduce CRC progression." The authors conclude "our study suggested that higher consumption of coffee after diagnosis was associated with lower CRC-specific and all-cause mortality in patients with stage I to III CRC."
Coffee consumption and selected gastrointestinal cancers morbidity in Poland. Jarosz M., Rychlik E., Sekula W. Annals of Nutrition and Metabolism 2017; 71 Supplement 2 (984). Poster	Meta-analysis	"The increase in coffee consumption in Poland could favourably affect some gastrointestinal cancers such as liver and gallbladder cancer morbidity rates in Poland and probably was one of the reasons of the observed decline in these cancers incidence in recent years. Furthermore positive (growing) trends in coffee consumption could influence the reduction in colorectal cancer incidence rate."
Coffee consumption and the risk of colorectal cancer by anatomical subsite in Japan: Results from the HERPACC studies. Senda Nakagawa H, Ito, Hosono S, Oze I, Tanaka H,	Case-control	"This meta-analysis of data from two of the largest case-control studies in Japanese populations found that coffee consumption was associated with a lower risk of colorectal cancer, particularly with a lower risk of distal colon cancer, and with a possible lower

Title & Reference	Type of Study	Author's conclusions & additional perspective
Matsuo K Int J Cancer. Jul. 15; 141(2):298-308		risk of rectal cancer. This study suggests that the impact of coffee on colorectal cancer prevention differs by colorectal anatomy." "These findings suggest that coffee consumption might impact the prevention of CRC, especially distal colon cancer."
Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Vieira AR, Abar L, Chan D, Vingeliene S, Polemiti E, Stevens C, Greenwood D, Norat T Ann Oncol. 2017 Aug. 1; 28(8):1788-1802.	Systematic Review and Meta-analysis	"Intakes of fruits, coffee, tea, cheese, poultry and legumes were not associated with colorectal cancer risk."
Coffee drinking and colorectal cancer risk: an evaluation based on a systematic review and meta-analysis among the Japanese population. Akter S, Kashino I, Mizoue T, Matsuo K, Ito H, Wakai K, Nagata C, Nakayama T, Sadakane A, Tanaka K, Tamakoshi A, Sugawara Y, Sawada N, Inoue M, Tsugane S, Sasazuki S Jpn J Clin Oncol. 2016 Aug.; 46(8):781-7.	Systematic Review and Meta-analysis	"From results of the present systematic review and meta-analysis, we conclude that the evidence is insufficient to support that coffee drinking increases or decreases colorectal cancer risk among the Japanese population."
Coffee Consumption and the Incidence of Colorectal Cancer in Women. Groessl EJ, Allison MA, Larson JC2, Ho SB, Snetslaar LG, Lane DS, Tharp KM,	Observational cohort	"Our results suggesting increased incidence of colorectal cancer associated with higher coffee consumption contradict recent meta-analyses but agree with a number of other studies showing that coffee increases risk or has

Title & Reference	Type of Study	Author's conclusions & additional perspective
Stefanick ML J Cancer Epidemiol. 2016; 2016:6918431.		no effect." "When breaking all colorectal cancers into the subtypes of colon, rectal and rectosigmoid, we did not find any significant relationship between regular coffee consumption [groups]."
Coffee Consumption and the Risk of Colorectal Cancer. Schmit SL, Rennert HS, Rennert G, Gruber SB Cancer Epidemiol Biomarkers Prev; 2016 Apr.; 25(4):634-9	Case-control	"This large case–control study provides evidence of an inverse, dose–response association between coffee drinking and the odds of colorectal cancer, colon, and rectal cancer incidence." "Global coffee consumption patterns suggest potential health benefits of the beverage for reducing the risk of colorectal cancer."
Coffee and cancer risk: A meta-analysis of prospective observational studies. Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H Sci Rep. 2016 Sept. 26; 6:33711.	Meta-analysis	The authors of this meta-analysis reviewed the results from 105 prospective cohort studies on the association between coffee and all cancer types. "Coffee intake was not significantly associated with colorectal cancer incidence in most subgroup analyses. However, an inverse relation was observed for colon cancer."

9. Liver Cancer

In our surveillance of the literature considered by IARC (from 2016-2018) there have been 9 studies looking at the relationship between coffee and liver disease. A number of these are reviews that analyze the findings and sometimes the actual data (e.g., meta-analysis) from the extensive literature database that exists for this endpoint. Some authors (Park et al. 2018) note that study designs are so large that this means millions of people have been studied. All nine of these studies were favorable for this endpoint, further supporting that coffee drinking appears to be associated with a lower risk of liver cancer. A few authors also note different demographics in their studies (White/Polish/Asian).

Table 9. Studies on coffee consumption and liver cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Prospective study of coffee consumption and cancer incidence in non-white populations. Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW Cancer Epidemiol Biomarkers Prev. 2018 Aug.; 27(8):928-935.	Prospective cohort	"Based on our prospective data in diverse populations, we found a decreased risk of liver …associated with higher coffee intake." "These results suggest that coffee drinking may protect against liver…cancer."
Protective effects of coffee consumption following liver transplantation for hepatocellular carcinoma Wiltberger G., Lange U., Hau H., Seehofer D., Krenzien F., Benzing C., Atanasov G., Pratschke J., Neumann U., Robson S., Schmelzle M. Zeitschrift fur Gastroenterologie 2018 56:1	In-vitro	Conclusion: "Coffee consumption is associated with a decreased risk of hepatocellular carcinoma (HCC) recurrence and provides for increased survival following orthotropic liver transplantation (OLT)."
Associations of Coffee Drinking and Cancer Mortality in the Cancer Prevention Study-II. Gapstur SM, Anderson RL, Campbell PT, Jacobs EJ, Hartman TJ, Hildebrand JS, Wang Y, McCullough ML Cancer Epidemiol Biomarkers Prev. 2017 Oct.; 26(10):1477-1486	Cohort	"These findings are consistent with many other studies that suggest coffee drinking is associated with a lower risk of … liver…cancer." "Finally, there is growing evidence that coffee consumption is associated with a lower risk of death from liver cancer. Our finding of a 21-25% lower risk with consumption of 4 or more cups/day is consistent with those of a large pooled analysis including nine prospective studies."
Coffee Consumption and Risk of Biliary Tract Cancers and Liver Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies Godos J, Micek A,	Meta-analysis	"The findings suggest that increased coffee consumption is associated with decreased risk of liver cancer, but not BTC." [biliary tract cancer] The authors go on to conclude that

Title & Reference	Type of Study	Author's conclusions & additional perspective
Marranzano M, Salomone F, Rio DD, Ray S Nutrients. 2017 Aug. 28; 9(9). pii: E950.		"coffee may represent a valid functional food for liver protection. Current evidence is sufficient to guide future clinical randomized trials to test the hepatoprotective effects of coffee, which in turn may lead to more definitive recommendations. However, further observational studies with better in-depth analyses of potential confounding factors are needed to test the association between coffee consumption and BTC."
Coffee: The magical bean for liver diseases. Heath RD, Brahmbhatt M, Tahan AC, Ibdah JA, Tahan V World J Hepatol. 2017 May 28; 9(15):689-696.	Review	"Coffee appears to reduce risk of hepatocellular carcinoma, reduce advancement of fibrotic disease in a variety of chronic liver diseases, and perhaps reduce [the] ability of hepatitis C virus to replicate. This review aims to catalog the evidence for coffee as universally beneficial across a spectrum of chronic liver diseases, as well as spotlight opportunities for future investigation into coffee and liver disease."
Coffee consumption and selected gastrointestinal cancers morbidity in Poland Jarosz M., Rychlik E., Sekula W. Annals of Nutrition and Metabolism 2017; 71 Supplement 2 (984) poster	Meta-analysis	"The increase in coffee consumption in Poland could favourably affect some gastrointestinal cancers such as liver and gallbladder cancer morbidity rates in Poland and probably was one of the reasons of the observed decline in these cancers' incidence in recent years."
Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J BMJ Open. 2017 May 9;	Meta-analysis	"Increased consumption of caffeinated coffee and, to a lesser extent, decaffeinated coffee are associated with reduced risk of hepatocellular cancer (HCC), including in pre-existing liver disease. These findings are important given the increasing incidence of HCC globally and its poor prognosis."

Title & Reference	Type of Study	Author's conclusions & additional perspective
7(5):e013739.		
A review of caffeine use as a risk or protective factor for women's health and pregnancy Peacock A., Mattick R.P., Bruno R. Curr. Opin. Psychiatry 2017; 30:4 (253-259)	Review	This study was focused on caffeine. Review of recently published studies does not suggest that current intake guidelines for adults and for pregnant woman need to be modified.
Coffee consumption and risk of hepatocellular carcinoma: a meta-analysis of eleven epidemiological studies. Bai K, Cai Q, Jiang Y, Lv L Onco Targets Ther. 2016 Jul. 19; 9:4369-75.	Meta-analysis	"The findings from this meta-analysis further confirmed the inverse association between coffee consumption and hepatocellular carcinoma risk with quantitative evidence. The protective effect can be detected among healthy population and patients with chronic liver diseases, and the consumption can also prevent the development of liver cirrhosis. Thus, the promotion of coffee consumption should be performed to reduce the risk of HCC. However, both biological research and epidemiological study should be further conducted to illustrate and validate the protective effect it renders."

10. Lung Cancer

Since the IARC evaluation, two recent studies have examined the relationship between coffee consumption and lung cancer. Neither study found an association between coffee consumption and an increased risk of lung cancer.

Table 10. Studies on coffee consumption and lung cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Coffee Consumption and Lung Cancer Risk: The Japan Public Health Center-Based Prospective Study. Narita S, Saito E, Sawada N, Shimazu T, Yamaji T, Iwasaki	Prospective cohort	"Our prospective study suggests that habitual consumption of coffee is not associated with an increased risk of lung cancer incidence, despite observing a significant increase in the risk for small cell carcinoma" (a tobacco-associated

Title & Reference	Type of Study	Author's conclusions & additional perspective
M, Sasazuki S, Noda M, Inoue M, Tsugane S J Epidemiol. 2017 Nov. 18.		malignancy, which might indicate residual confounding). "This positive association was substantially attenuated after adjusting for cigarette smoking. Further evidence is needed to determine the associations with subtypes of lung cancer. Future studies that capture more detailed quantitative information on tobacco exposure would help clarify the impact of residual confounding on lung carcinogenesis."
The consumption of coffee and black tea and the risk of lung cancer. Pasquet R, Karp I, Siemiatycki J, Koushik A Ann Epidemiol. 2016 Sept. 17. pii: S1047-2797(16)30308-8. 10.1016/j.annepidem.2016.09.001	Case-control	"This population-based case-control study did not find any strong association between daily coffee … consumption in adults and a risk of lung cancer." "For coffee, our results are suggestive that low consumption may decrease the risk of lung cancer." Authors inquired on lifetime coffee consumption (not just consumption at baseline) and duration of consumption, and collected detailed smoking information.

11. Oral Cancer

In our surveillance of the literature post-IARC (from 2016-2018) there have been two studies looking at the relationship between coffee and oral cancer. Both studies showed an inverse association, indicating a potentially protective effect, of coffee consumption on the risk or incidence of oral cancer. One of the studies concluded the same for pharyngeal cancer as well. Both studies were meta-analyses of previously published case-control and cohort studies; Li, et al. included just over 5000 cases.

Table 11. Studies on coffee consumption and oral cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Coffee is protective against oral and pharyngeal cancer: A systematic review and meta-analysis. Miranda J, Monteiro L, Albuquerque R, Pacheco JJ, Khan Z, Lopez-Lopez J, Warnakulasuryia S Med Oral Patol Oral Cir Bucal. 2017 Aug. 15:0.	Meta-analysis	"We can conclude that the results obtained from this meta-analysis confirm that there is an inverse association between high coffee consumption and the risk of oral/pharyngeal cancer, so we can infer that individuals who consume higher amounts of coffee are less likely to develop oral cancer. However, in the future, it may be necessary to determine the robustness of the results obtained in this study and to thus confirm the inverse association demonstrated, as well as establishing greater rigour and consistency between variables and co-variables, especially tobacco and alcohol."
Coffee consumption associated with reduced risk of oral cancer: a meta-analysis Li YM, Peng J, Li LZ Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Apr.; 121(4):381-389.e1.	Meta-analysis	"The results from this meta-analysis indicated that high consumption of coffee can significantly reduce the risk of oral cancer. However, findings of this meta-analysis should be treated with caution because of potential biases and confounders. Further prospective studies to confirm our results should be stricter about confounding variables, such as smoking and alcohol consumption, which are environmental and social risk factors for the development of oral cancer."

12. Prostate Cancer

Since the IARC evaluation, there have been seven studies looking at the relationship between coffee consumption and prostate cancer. All but one of the studies found evidence that coffee consumption was associated with a decreased risk of prostate cancer. Authors used phrases such as "coffee can be part of a healthful diet" and "coffee may reduce the risk of cancer progression."

Table 12. Studies on coffee consumption and prostate cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Dietary Consumption of Phenolic Acids and Prostate Cancer: A Case-Control Study in Sicily, Southern Italy. Russo GI, Campisi D, Di Mauro M, Regis F, Reale G, Marranzano M, Ragusa R, Solinas T, Madonia M, Cimino S, Morgia G. Molecules. 2017 Dec. 5; 22(12). pii: E2159.	Case-control	This population-based case-control study found that high intake of caffeic acid and ferulic acid were significantly associated with reduced risk of prostate cancer in the Mediterranean study population. Coffee was one of many dietary sources of phenolics measured in the study. The authors cautioned that "the complexity of phenolic acids composition is complex. In fact, food frequency questionnaires which assess dietary habits may lead to measurement errors."
Coffee and tea consumption and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition Sen A, Papadimitriou N, Lagiou P, Perez-Cornago A, Travis RC, et al. Int J Cancer. 2018 Jun 26.	Prospective cohort	"No evidence of association was seen for consumption of total, caffeinated or decaffeinated coffee … and risk of total prostate cancer or cancer by stage, grade or fatality in this large cohort." As in other studies, "information on coffee … intake was self-reported only at recruitment, which will inevitably be imperfect."
Coffee, Caffeine, and Health Outcomes: An Umbrella Review Grosso G, Godos J, Galvano F, Giovannucci EL Annu Rev Nutr. 2017 Aug. 21; 37:131-156.	Review	The authors reported that "coffee was associated with a probable decreased risk of … prostate [cancer]" and concluded: "Given the spectrum of conditions studied and the robustness of many of the results, these findings indicate that coffee can be part of a healthful diet."
Reduction by coffee consumption of prostate cancer risk: Evidence from the Molisani cohort and cellular models Pounis G, Tabolacci C, Costanzo S, Cordella M, Bonaccio M, Rago L, D'Arcangelo D, Filippo Di Castelnuovo A, de Gaetano G, Donati MB, Iacoviello L,	Prospective cohort	The authors concluded: "reduction by Italian-style coffee consumption of prostate cancer risk (>3 cups/day) was observed in epidemiological level." Authors cited a small number of cases and short follow-up period as limitation.

Title & Reference	Type of Study	Author's conclusions & additional perspective
Facchiano F; Moli-sani study investigators Int J Cancer. 2017 Apr. 24.		
Investigating the possible causal role of coffee consumption with prostate cancer risk and progression using Mendelian randomization analysis Taylor AE, Martin RM, Geybels MS, Stanford JL, et al. Int J Cancer. 2017 Jan. 15; 140(2):322-328.	Case-control Mendelian randomization analysis	The authors' findings "are not consistent with a substantial effect of coffee consumption on reducing prostate cancer incidence or progression." There were many limitations inherent to the study protocol, including, "statistical power to detect associations in Mendelian randomization studies is substantially lower than conventional observational analyses."
An Up-to-date Meta-analysis of Coffee Consumption and Risk of Prostate Cancer. Xia J, Chen J, Xue JX, Yang J, Wang ZJ Urol J. 2017 Aug. 29; 14(5):4079-4088	Meta-analysis	CC= coffee consumption PC = prostate cancer "Our results indicate that coffee consumption has no harmful effect on prostate cancer. On the contrary, it has an effect on reducing the localized PC risk. Further prospective cohort studies of high quality are required to clarify this relationship." Authors included as many studies as they could and cited this as an advantage along with their dose-response analysis. Limitations included the following: "heterogeneity among studies may have been involved because of methodological differences among studies, including different methods of coffee preparation, misclassification of CC differences in serving size and brew strength."

Title & Reference	Type of Study	Author's conclusions & additional perspective
Prostate cancer progression and mortality: a review of diet and lifestyle factors Peisch SF, Van Blarigan EL, Chan JM, Stampfer MJ, Kenfield SA Food Chem. 2016 Dec. 15; 213:251-9.	Review	This review investigated the impact dietary and lifestyle effects have on prostate cancer, based on evidence from epidemiologic studies. The authors state that "coffee may also have a role in reducing risk of prostate cancer progression." The authors found that multiple studies and meta-analyses reported an association between coffee (both decaffeinated and caffeinated) consumption and a significant reduction of developing lethal prostate cancer, with greater reduction in men consuming ≥ 6 cups per day.

13. Non-Melanoma Skin Cancer

Eight recent studies since the IARC evaluation have examined the relationship between coffee consumption and skin cancer. Although all of the studies found an inverse association between coffee consumption and risk of cancer, the majority of the more recent studies were focused on non-melanoma skin cancer. Some of the authors used the term "chemopreventive" in describing the effect of coffee on basal cell carcinoma. Reviews were the prominent type of study identified and hundreds of thousands of people were followed with tens of thousands of cases of skin cancer studied. The chemopreventive effect seems to be associated with caffeinated coffee only.

Table 13. Studies on coffee consumption and skin cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
An epidemiological review of diet and cutaneous malignant melanoma. Yang K, Fung T, Nan H. 2018 Jul. [Epub ahead of print.]	Review	This review article finds that current epidemiological evidence suggests that higher caffeine intake and caffeinated coffee consumption may help reduce melanoma risk. The review looked at a wide range of dietary exposures.

Title & Reference	Type of Study	Author's conclusions & additional perspective
Prospective study of coffee consumption and cancer incidence in non-white populations Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW Cancer Epidemiol Biomarkers Prev. 2018 Aug.; 27(8):928-935.	Prospective cohort	"Based on our prospective data in diverse populations, we found a decreased risk of … melanoma associated with higher coffee intake." "During a mean follow-up of 15.3 years, 34,031 incident [all] cancer cases were identified among study participants. Coffee intake was associated inversely with … melanoma."
Coffee consumption and risk of nonmelanoma skin cancer: A dose-response meta-analysis Vaseghi G., Haghjoo-Javanmard S., Naderi J., Eshraghi A., Mahdavi M., Mansourian M. European Journal of Cancer Prevention 2018; 27:2 (164-170)	Meta-analysis	This meta-analysis suggested that "caffeinated coffee might have chemopreventive effects against basal cell carcinoma dose dependently." The authors suggested that in the meta-analysis of published studies, "publication bias may contribute toward a biased false-positive relationship as small-studies with null results may not be published."
Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis Caini S, Cattaruzza MS, Bendinelli B, Tosti G, Masala G, Gnagnarella P, Assedi M, Stanganelli I, Palli D, Gandini S European Journal of Nutrition 2017; 56:1	Meta-analysis	Basal Cell Carcinoma = BCC "Coffee intake appears to exert a moderate protective effect against BCC development, probably through the biological effect of caffeine. However, the observational nature of studies included, subject to bias and confounding, suggests taking with caution these results that should be verified in randomized clinical trials."
Coffee, tea and melanoma risk: Findings from the European Prospective Investigation into Cancer and Nutrition Caini S., Masala G., Saieva C., Kvaskoff M., Savoye I., et al. International Journal of Cancer. 2017.	Prospective cohort	"The consumption of caffeinated coffee was inversely associated with melanoma risk among men in this large cohort study" that also had a long follow-up. There were no statistically significant associations between consumption of decaffeinated coffee … and the risk of melanoma among both men and women. The study did not attempt to measure sun exposure.

Title & Reference	Type of Study	Author's conclusions & additional perspective
Caffeinated and decaffeinated coffee consumption and melanoma risk: a dose-response meta-analysis of prospective cohort studies Micek A, Godos J, Lafranconi A, Marranzano M, Pajak A Int J Food Sci Nutr. 2017 Sept. 11:1-10.	Meta-analysis	"An increase in coffee consumption of one cup per day was associated with a 3% reduction in melanoma risk." The authors conclude: "Results from this dose-response meta-analysis indicate that coffee consumption is inversely associated with melanoma risk." Authors used a dose-response meta-analysis methodology (strength) but stated that not all studies categorized exposure in the same way (limitation).
A review of caffeine use as a risk or protective factor for women's health and pregnancy Peacock A., Mattick R.P., Bruno R. Curr. Opin. Psychiatry 2017; 30:4 (253-259)	Review	"Based on predominantly observational studies, moderate caffeine intake has been shown to be a protective factor for … skin cancer." This review of recently published studies does not suggest that current intake guidelines for adults and for pregnant woman need to be modified.
Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis Caini S, Cattaruzza S, Bendinelli B, Tosti G, Masala G, Gnagnarella P, Assedi M, Stanganelli I, Palli D, Gandini S Eur J Nutr. 2016 Jul. 7.	Meta-analysis	"Coffee intake appears to exert a moderate protective effect against Basal Cell Carcinoma development, probably through the biological effect of caffeine. However, the observational nature of studies included, subject to bias and confounding, suggests taking with caution these results that should be verified in randomized clinical trials." No effect was seen for decaffeinated beverages.

14. Uterine and Ovarian Cancer

In our surveillance of the literature post-IARC (from 2016-2018) there have been ten studies looking at the relationship between coffee consumption and endometrial, ovarian, or uterine cancers. Specific populations studied included Canadian, African American, Native Hawaiian, Japanese Americans, Latinos, whites, and post-menopausal women. Only one study reported that their conclusions remained unclear; the remainder concluded inverse relationships (higher coffee consumption was associated with lower cancer risk). Bamia et al., 2017 looked specifically at what the IARC working group reviewed and concluded that not only was there

lower risk of endometrial cancer, but then went on to state that their findings are of high public health importance.

Table 14. Studies on coffee consumption and uterine and ovarian cancer

Title & Reference	Type of Study	Author's conclusions & additional perspective
Associations of coffee, tea and caffeine intake with risk of breast, endometrial and ovarian cancer among Canadian women Arthur R., Kirsh V.A., Rohan T.E. Cancer Epidemiol. 2018; 56: (75-82)	Prospective cohort	"Our study supports existing evidence which indicates that coffee consumption may be associated with reduced risk of endometrial cancer." A "limitation in this study was the small number of events for endometrial and ovarian cancer, such that we could not assess the modifying effects of menopausal status, HRT use and adiposity on the associations."
Coffee consumption is not associated with ovarian cancer risk: A dose-response meta-analysis of prospective cohort studies Berretta M., Micek A., Lafranconi A., Rossetti S., Di Francia R., De Paoli P., Rossi P., Facchini G. Oncotarget 2018; 9:29 (20807-20815)	Meta-analysis	This comprehensive meta-analysis did not find evidence of an association between the consumption of coffee and risk of ovarian cancer. The authors suggest a "potential confounding effect of other foods" may have affected their results. However, "A major strength of our meta-analysis was the inclusion of cohort studies carried out with a prospective design, which implies detailed exposure and covariate assessment before the diagnosis of the outcome of interest (that is, ovarian cancer)."
Coffee Drinking and the Risk of Endometrial Cancer: An Updated Meta-Analysis of Observational Studies Lukic M., Guha N., Licaj I., van den Brandt P.A., Stayner L.T., Tavani A., Weiderpass E. Nutrition and Cancer 2018; 70:4 (513-528)	Meta-analysis; 20 total studies (12 cohort, 8 case-control); 2,746 cases	"The results from our meta-analysis strengthen the evidence of a protective effect of coffee consumption on the risk of endometrial cancer and further suggest that increased coffee intake might be particularly beneficial for women with obesity." While the study was very large, the authors concede that included studies may have had unknown confounders. Coffee consumption was self-reported in all studies.

Title & Reference	Type of Study	Author's conclusions & additional perspective
Prospective study of coffee consumption and cancer incidence in non-white populations Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW Cancer Epidemiol Biomarkers Prev. 2018 May 18.	Prospective cohort; 427 ovarian cancer cases	"Based on our prospective data in diverse populations, we found a decreased risk of … ovarian … and endometrial cancers … associated with higher coffee intake." The large, diverse population, long follow-up period, and ability to control for confounding were strengths. Exposure was measured by questionnaire; some participants completed a follow-up questionnaire as well.
Assessment of moderate coffee consumption and risk of epithelial ovarian cancer: a Mendelian randomization study Ong JS, Hwang LD, Cuellar-Partida G, Martin NG, Chenevix-Trench G, Quinn MCJ, Cornelis MC, Gharahkhani P, Webb PM, MacGregor S; Ovarian Cancer Association Consortium. Int J Epidemiol. 2018 Apr. 1; 47(2):450-459.	Case-control Mendelian randomization analysis	When examining the DNA of cases and controls, the authors found "no evidence indicative of a strong association between EOC (endometrial and ovarian cancer) risk and genetically predicted coffee or caffeine levels. However, our estimates were not statistically inconsistent with earlier observational studies and we were unable to rule out small protective associations."
Coffee intake and risk of breast and ovarian cancer: Updated systematic review and meta-analysis Bamia C., Turati F., Guercio V., Guha N., Loomis D., Tavani A. Annals of Nutrition and Metabolism 2017; 71 Supplement 2 (950-951)	Meta-analysis of all studies in the IARC working group report; 72 studies total	Findings from this updated meta-analysis suggest no association with ovarian cancer risk. "These associations did not differ by study design, geographical location or menopausal status (both cancer sites) … or histological type (ovarian cancer)."
Coffee Decreases the Risk of Endometrial Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies Lafranconi A, Micek A, Galvano F, Rossetti S, Del Pup L, Berretta M, Facchini G Nutrients. 2017 Nov. 9; 9(11). pii: E1223.	Meta-analysis of 12 studies	"Our findings suggest that increased coffee consumption is associated with decreased risk of endometrial cancer, and this association is observed also for postmenopausal cancer." The study did not measure potential changes in exposure level over time.

Title & Reference	Type of Study	Author's conclusions & additional perspective
Coffee, Caffeine, and Health Outcomes: An Umbrella Review Grosso G, Godos J, Galvano F, Giovannucci EL Annu Rev Nutr. 2017 Aug. 21; 37:131-156.	Meta-analysis of 112 observational studies	Of the 59 unique outcomes examined in the selected 112 meta-analyses of observational studies, coffee was associated with a probable decreased risk of endometrial cancer, among others. "Given the spectrum of conditions studied and the robustness of many of the results, these findings indicate that coffee can be part of a healthful diet."
Tea, coffee, and caffeinated beverage consumption and risk of epithelial ovarian cancers. Leung AC, Cook LS, Swenerton K, Gilks B, Gallagher RP, Magliocco A, Steed H, Köbel M, Nation J, Brooks-Wilson A, Le ND. Cancer Epidemiol. 2016 45:119-125.	Population-based case control	"No excess risk was seen for coffee or caffeinated soft drinks." Lifetime adult exposure was calculated from a one-time interview or questionnaire. "The risk estimates were adjusted for known and suspected confounders such as smoking and alcohol consumption as well as parity, and other ovarian cancer risk factors;" although authors acknowledged that recall bias could be a factor.
Dietary total antioxidant capacity in relation to endometrial cancer risk: a case–control study in Italy Rossi M, Tavani A, Ciociola V, Ferraroni M, Parpinel M, Serafini M, Bellocco R, Zucchetto A, Montella M, Serraino D, Lagiou P, La Vecchia C Cancer Causes Control. 2016 Mar;27(3):425-431.	Case-control; 454 cases of endometrial cancer in Italian population	The researchers found that dietary total antioxidant capacity was inversely related to endometrial cancer risk, and coffee seemed to be a contributing factor for both its antioxidants and possibly other beneficial components. "Our findings suggest a favorable role of a diet high in TAC on endometrial cancer risk, which can be partially driven by coffee consumption." Exposure information was collected by questionnaire.

15. "Other" cancer sites

Since IARC's re-evaluation, there have been three cancer endpoints addressed by one study each, thus for ease of reading we have grouped these into a category designated as "other". As shown by the authors' statements below, all of these suggested coffee was not associated with increased cancer risk and may even be protective.

Table 15. Studies on "other" cancer sites

Title & Reference	Type of Study	Author's conclusions & additional perspective
Effect of coffee consumption on **cholangiocarcinoma** risk and survival Jaruvongvanich V., Yang J.D., Peeraphatdit T., Roberts L.R Gastroenterology 2017; 152:5 (S1176)	Case-control	CCA= cholangiocarcinoma "Coffee intake was neither associated with risk of cholangiocarcinoma (CCA) development nor with risk of death in patients with CCA." In fact, authors "observed trends toward a protective effect of coffee on the risk of CCA."
Coffee Consumption and Risk of **Gallbladder Cancer** in a Prospective Study Larsson SC, Giovannucci EL, Wolk A J Natl Cancer Inst. 2017 Mar. 1; 109(3):1-3. doi: 10.1093/jnci/djw237.	Prospective cohort	Based on 74 gall bladder cancer cases in a population of over 72,000 Swedish adults, authors concluded that "coffee consumption is associated with a reduced risk of gallbladder cancer."
Coffee Consumption and the Risk of **Thyroid Cancer**: A Systematic Review and Meta-Analysis Han MA, Kim JH Int J Environ Res Public Health. 2017 Jan. 27; 14(2). pii: E129. doi: 10.3390/ijerph14020129	Meta-analysis	Authors found "no significant association between coffee consumption and thyroid cancer risk according to our meta-analysis results." However, the authors cautioned that "these findings should be interpreted with caution because of potential biases and confounding variables."

* * *

In conclusion, the overwhelming weight of scientific evidence strongly supports OEHHA's determination that exposures to Proposition 65 listed chemicals in coffee that are produced as part of, and inherent in the process of roasting coffee beans and brewing coffee, pose no significant risk of cancer.

Thank you for considering our comments.

Sincerely,

Mark Corey, Ph.D.
Director of Scientific & Government Affairs
National Coffee Association of USA, Inc.

Alan Leviton, MD
Consultant to the NCA Scientific Advisory Group